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Angina-like Pain: A Manifestation of the Male Climacterium

THOMAS HODGE MCGAVACK, M.D.

From the New York Medical College and the Endocrine and Metabolic Service of the Metropolitan Hospital, New York City

IN BOTH THE MALE and the female, at some period of life, a readjustment normally occurs in the body secondary to a change in the entire system of endocrine glands as a result of a lessening activity of the gonads. This change frequently takes place without distressing or untoward manifestations other than those to be expected as an integral part of the aging process. However, in a certain proportion of individuals, any of a number of unpleasant reactions may occur which are not infrequently confused with disease entities of one type or another. To such disturbances we apply the term climacterium, and in this sense it is used here.

In a certain proportion of women the presence of the climacterium is generally acknowledged, perhaps because the cessation of ovulation and menstruation marks an episode in, but is not necessarily either the beginning or the end of that critical period. Fluhmann (1) and Scherf (2) have both emphasized the fact that symptoms of the climacterium are frequently manifest long before menstruation ceases, and in other instances may not appear until years after that event has occurred.

In men there is no such dramatic circumstance to punctuate the course of events associated with gradually declining sexual activity and muscular vigor. Moreover, for some time it has been recognized that an abrupt decrease in male hormone is not likely to occur at any particular age (3, 4).

In the present state of our knowledge, however, it hardly seems possible to look upon the estimation of various hormones in body fluids as the determining factor in categorizing the rather distressing complaints attendant upon the period of life in question. One needs to call to mind only the fact that estrogens and androgens are produced in relatively large amounts from extragonadal sources in both the male and the female to appreciate the force of this statement. Furthermore, too little is at present known regarding the relative amounts of gonadotropins, estrogens, and androgens present during the climacterium in either the male or the female to regard dogmatically any par-

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ticular set of values for these substances as prerequisite to such a diagnosis.

Therefore, until further hormonal studies are available, the subjective complaints of the patient will continue to be of paramount importance in determining therapy. The symptoms of the climacterium may be general and include malaise, lack of interest, easy tiring, mentally and physically, and a 'general rundown feeling.' On the other hand, a particular system or part of the body may bear the brunt of the disturbance. In this category we must include the psychoses, particularly the depressive states and melancholias, unstable vasomotor reactions, genito-urinary complaints, and myalgic and arthritic disturbances. To these must be added the cardiac syndrome of the climacterium, already well recognized in the female (2, 5), but thus far not stressed in the male. Without making any attempt to draw hard and fast conclusions, we have felt it justifiable to record our observations, from which a distinct clinical entity may emerge in the hands of subsequent investigators.

CASE REPORTS

Case 1, H.C.M., male, aged 53, was first seen Sept. 4, 1941, at which time he complained of sudden, sharp pains in the left chest radiating down the left arm to the finger tips. He stated that he had had his first attack of such pain about Aug. 1, 1941, following the exertion of running for a train. Since this incident he had suffered continuously from a sense of oppression over the precordium. Occasionally there had been a return of the severe pain without definite relation to exercise.

On physical examination there was no evidence of cardiac disease.

His electrocardiogram before and after exercise revealed a normal sinus rhythm and a pulse rate of 74. There were some variations in contour of the P-wave in *lead 1*, but no change in the P-R interval or any similar changes in other leads, so that this point was probably not significant. Left-axis deviation due to a large S-3 and slurring of the intrinsic deflection in the chest leads amounting to a notch in lead CR_2 were the only questionable alterations.

The patient was given rectal suppositories of aminophyllin, 7.5 grains each, twice a day, and 1/100 grain tablets of nitroglycerin as necessary for attacks of acute pain.

When next seen, Sept. 14, 1941, he had experienced a steady, continuous, severe pain over the precordial and sternal areas of two days' duration. Neither this nor any other sharp attacks of pain had been relieved by the tablets of nitroglycerin. A diagnosis of coronary thrombosis was considered, but no clinical evidence of it could be obtained. Testosterone propionate,[1] 25 mg., was administered subcutaneously with complete relief of symptoms by the following morning. This was followed by a series of 6 injections at twice-weekly intervals. Injections were then given at twice-weekly intervals for 2 months, following which they have been made at from 1 to 6-week intervals to date (Nov. 1, 1942) whenever any 'distress' has been noted. With each recurrence, testosterone therapy has given prompt and complete relief.

Comment. The syndrome above detailed apparently corresponds in all its particulars to the cardiac neurosis commonly seen in the human female at the menopause.

Case 2, P.B., a 37-year-old male, was first seen March 15, 1941, complaining of fullness in the epigastrium which was worse after dinner and at night, and was accompanied by much belching and the passing of flatus. Associated symptoms were breathlessness, not connected with exercise, palpitation of the heart of 6 months' duration, and pains through the left side of his chest, particularly in the third, fourth, and fifth interspaces to the left of the sternum. These symptoms had begun several months before, and recurred occasionally until 3 weeks prior to his first visit, since which time they had been recurring daily. He stated that he had a great many sighing respirations. There was no insomnia. Laboratory studies including urinalysis, complete blood count, blood sugar, blood cholesterol, and roentgen studies of the heart and lungs were all performed, with essentially normal findings. The basal metabolic rate was −18 per cent. The electrocardiogram before and after exercise on March 17, 1941, revealed a normal sinus mechanism, a pulse rate of 65 per minute, and a somewhat low voltage of QRS complexes in each of the limb leads. There were no conduction defects or axis deviations.

A diagnosis of gastro-intestinal neurosis and of the climacterium was made. Because of the low metabolic rate, the patient was given desiccated thyroid substance. Two months later, in addition to thyroid extract, he was given bellergal because of the spasmodic, cramp-like pains felt over the epigastrium, often in relation to meals. The thyroid substance was continued until Oct. 2, 1941, when he complained bitterly of weakness, listlessness, pain, diminished libido, and 'shortness of breath,' not related to exercise or time of day.

A single hypodermic injection of testosterone propionate, 25 mg., was followed by complete relief of all symptoms for 3 days. Six injections were then made at 5-day intervals. Thereafter, treatment with 25 mg. doses was given as necessary. Intervals between doses have varied from 5 days to 4 weeks. None of the severe symptoms has recurred to date (Nov. 1, 1942).

[1] The testosterone propionate in sesame oil for injection and the compressed tablets of crystalline testosterone for implantation used in this and all other cases were supplied by Dr. Max Gilbert, of the Schering Corp., Bloomfield, N. J.

Comment. The possibility of climacteric symptoms was recognized in this patient at the time of his first visit. However, in line with the work of Kreutzmann (6), it was thought that the thyroid might be primarily at fault, particularly in view of the lowered metabolic rate. Thyroid medication was totally ineffective, and only after its failure to relieve symptoms was the lowered metabolism accepted as a secondary feature of the gonadal disturbance (7,8).

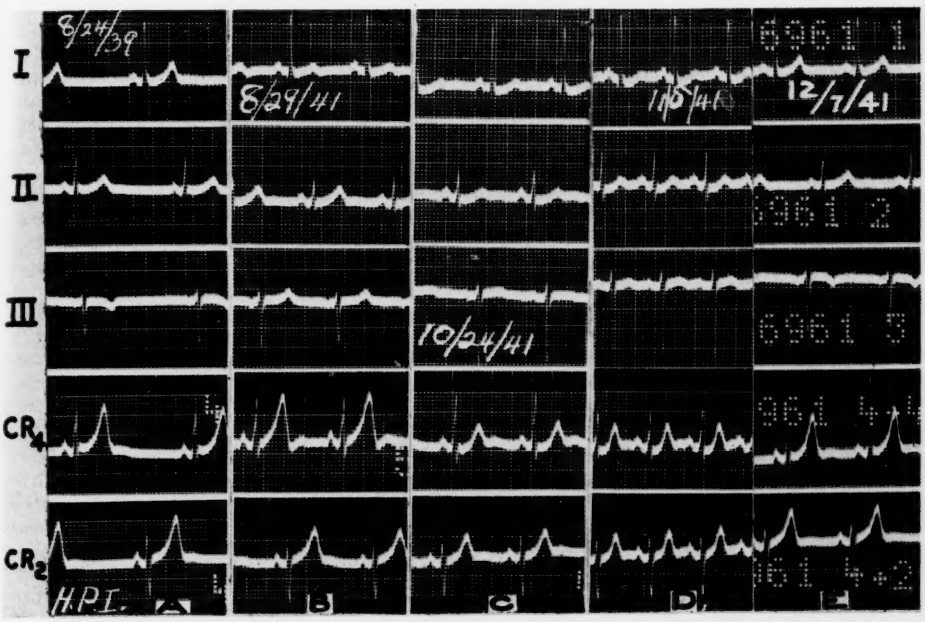

Fig. 1. *Case 3.* ELECTROCARDIOGRAPHIC TRACINGS.

A Normal electrocardiogram, August, 1939, during initial illness.
B Third attack of cardiac nature, August, 1941; note low T-1 and slightly downward terminal deflection of T-1 and T-CR_4.
C October 24, 1941, before any testosterone therapy; striking features are the sagging R-T segment in *leads 1, 2,* and CR_4 and the diminished T-waves in all leads.
D November 11, 1941, after 75 mg. of testosterone propionate intramuscularly and an implant of 300 mg. of crystalline testosterone; tracing appears much as before therapy except for increased rate; testosterone effect was not reflected in the electrocardiogram.
E December 7, 1941, complete normalization of the electrocardiogram has taken place under the influence of hormonal treatment.

However, the blood pressure did not fall; no fever developed during his stay in the hospital.

In September, 1939, he had a recurrence of severe symptoms, but physical examination and laboratory findings failed to establish a more satisfactory diagnosis than that previously made.

The patient was re-admitted on June 18, 1940, and again on August 28, 1941, with an intensification of all his previously mentioned symptoms. In addition, he complained of insomnia, of dull, frequently recurring headaches, and of shifting, neuralgic pains in the legs and arms. During the second of these admissions the

Case 3, H.P.I., a 54-year-old man, was admitted to the hospital on Aug. 23, 1939, following a fainting spell. Marked weakness, a feeling as though 'passing out,' a 'pins-and-needle' sensation in all extremities, a dull, aching, continuous, precordial pain, and mild epigastric distress characterized the attack. An electrocardiogram taken at that time showed a sinus bradycardia. The rate of sedimentation of erythrocytes was high, 30 mms. in one hour (Westergren method). In spite of the normal electrocardiogram (fig. 1A), it was thought that he had suffered a mild attack of coronary occlusion, for which treatment was instituted. How-

paresthesias in the lower extremities were so marked as to justify a diagnosis of early peripheral neuritis, for which, however, no underlying cause could be discovered.

Repeated electrocardiographic tracings taken before and after exercise were uninformative until that taken on Aug. 29, 1941 (fig. 1B). At that time there was a normal sinus mechanism with a pulse rate of 78 per minute. There were no conduction defects. Left-axis deviation was present. As compared with the record of Aug. 24, 1939, the following changes were evident: *Lead 1:* The T-wave was lower with a very

slight terminal downward dip, hardly enough to be called diphasic, but not normal in contour. *Lead 3:* The T-wave was upright, whereas formerly it had been depressed. *Lead* CR_4: A slight downward dip appeared at the end of the T-wave, which had not been present before. In *lead* CR_2 the T-wave was taller, a quantitative change of doubtful significance.

In view of the still-high sedimentation rate, for which no reason could be found, and the changes in the electrocardiogram, the patient was advised to take a vacation. Upon his return to the city on Oct. 24, 1941, there had been no improvement whatsoever, and his arthralgias, myalgias, and insomnia appeared even more intense than before. Further abnormal changes were evident in his electrocardiogram taken as of that date (fig. 1C). In *lead 1* there was sagging of the R-T segment; this appeared in a slight degree also in *leads 2* and CR_4. The T-waves throughout were smaller than before. The patient had not received digitalis at any time during the period of observation.

This electrocardiogram suggested that seen frequently in the climacterium of women, and the patient was immediately given 25 mg. of testosterone propionate. On Oct. 27, 1941 he reported improvement in all of his symptoms, had found his energy high on October 25 and 26, and had lost the pains through his chest. Two subsequent doses were given on October 27 and 29, respectively, following which all his symptoms had disappeared, and he asked to be allowed to return to work. An implant of 300 mg. of testosterone as 75-mg. pellets was then made subcutaneously. On indication of return of symptoms, this has been repeated twice since that time. An electrocardiogram made on Nov. 5, 1941 (fig. 1D), showed a slight increase in heart rate and little or no change from the preceding abnormal record. A tracing on Dec. 7, 1941 (fig. 1E), showed a completely normalized pattern. Subsequent electrocardiograms (three in number) have also been normal.

Comment. This is the only one of 8 patients who has shown changes in his electrocardiogram similar to those seen repeatedly in connection with the climacterium of women (2, 5). The proof that these changes are an integral part of the syndrome is their disappearance with all the other symptoms following adequate therapy.

Case 4, L.S.,[2] a 44-year-old man, first seen Jan. 6, 1942, had complained intermittently since the age of 19 of pains through the left chest extending into the left arm. For the 6 to 8 months preceding his first visit, this had recurred several times daily and was of a dull, aching character, associated with extreme irascibility. Its onset, severity, and progression were not related to effort, meals, time of day, or degree of tiredness. For 6 months he had been completely impotent. His habits were exemplary. The past history was irrelevant. His father had died at the age of 52 as a result of 'angina pectoris and nephritis.'

He was a short, stocky, moderately overweight person with a somewhat pasty complexion. There was slight exophthalmos, although the thyroid was not enlarged. The heart was normal in size, shape, position and action. The pulse rate was 84 per minute. His blood pressure when lying down was 150 mm. Hg systolic, 96 diastolic, and when sitting was 128 and 94 mm. Hg. The prostate was small, firm, and showed no nodules.

The basal metabolic rate was −1.6 per cent. No sighing respirations were present during the test. Roentgen examination of the heart and lungs revealed no abnormal findings. The electrocardiogram showed a normal sinus mechanism with a predominant rate of 70 per minute. There were no conduction defects. There was a moderate left-axis deviation which, in view of the inverted T-3 wave, was ascribed to the transverse position of the heart. During the 6 months prior to the time we first saw him, this patient had received aminophyllin, nitroglycerin, and other vasodilators as well as digitalis, none of which in any way affected his cardiac status. In view of his impotence and the failure of therapy directed toward improving cardiac circulation, it was our opinion that the patient was suffering from symptoms associated with the climacterium. Twenty-five mg. of testosterone propionate were given 3 times weekly for 2 weeks, and then twice weekly for the ensuing 3 weeks. He was completely relieved of symptoms until approximately 4 weeks following the last injection, at which time (March 27, 1942) an implant of 300 mg. of crystalline testosterone was made.[3] To date (Nov. 1, 1942) the patient has had no return of the distressing symptoms.

Comment. The longstanding cardiac symptoms of purely functional origin, the failure to obtain relief from vasodilator drugs, and the presence of impotence made the diagnosis of this patient's condition relatively easy.

The statement has been made that the climacterium may begin at puberty and end with death. This patient is convincing testimony to the fact that the endocrine maladjustment which gives rise to symptoms of the climacterium may make its appearance at an early age and continue indefinitely without abatement or until such time as specific therapy is applied.

Case 5, G.E.H., a 40-year-old man, first seen Sept. 28, 1936, complained of 'acid erosion of the teeth,' noted 2 months previously, and 'numbing' precordial pain radiating to both arms first experienced one month before. He stated that he smoked an occasional

[2] This patient was seen through the courtesy of Dr. Dewitte R. S. Barnes.

[3] We have estimated the average time for complete absorption of each pellet to be approximately 80 to 90 days, so that each yields between 0.8 and 0.9 mg. of material per day

cigar and used alcohol sparingly. He was of athletic build and tendency. Physical examination revealed no abnormalities except for marked gingival erosion of the buccal surfaces of nearly all his teeth.

Urinalysis and blood count revealed no abnormal findings. Total blood protein was 6.10 mg. per cent; blood inorganic calcium, 9.10 mg. per cent; phosphorus, 2.8 mg. per cent; and phosphatase, 4.2 Bodansky units. The blood Wassermann reaction was negative.

Following the use of a high-calcium, high-vitamin diet yielding 2500 calories daily, and a daily intake of 2 gm. of calcium gluconate, 25,000 units of vitamin A, and 5100 units of vitamin D, most of his symptoms disappeared. This regime was continued until April, 1937, when total blood-plasma protein was 6.4 mg. per cent, blood inorganic calcium, 10.5 mg. per cent; and phosphorus, 3.8 mg. per cent.

The patient was not seen again until Jan. 21, 1942, by which time he had had a return of all his previous complaints except that his teeth had given him no further trouble. In addition, however, he was easily made irascible, and thought he had 'kidney trouble' because of nocturia and a feeling of insecurity of the bladder sphincter.

At this time the blood pressure was 104 mm. Hg systolic, 70 diastolic. The prostate was enlarged, whereas previously it had been normal in size; its consistency was unchanged.

The blood count and urinalysis showed no abnormal findings. Blood calcium was 10.6 mg. per cent; phosphorus, 3.2 mg. per cent; and total protein, 6.6 mg. per cent.

Roentgen-ray study of the heart and lungs revealed no pathology. An electrocardiographic tracing showed a normal sinus mechanism with a rate of 60 per minute. The RST segment was elevated slightly in *leads 1* and *2* with an upward convexity. In view of the slow rate, however, this was interpreted as a personal peculiarity rather than as significant of an inflammatory process in the pericardium.

The patient was given two injections of testosterone propionate, 25 mg., at 2-day intervals with relief of the tiredness, urinary symptoms and chest pain. Methyl testosterone was then prescribed in a dose of 10 mg. daily. The patient continued this regime for 4 weeks. He had no further treatment until June 4, 1942, when most of his symptoms had returned, particularly the discomfort under the sternum and the fatigue. These were again relieved by testosterone propionate, and methyl testosterone by mouth was prescribed as before. At the present time (Nov. 1, 1942) the patient takes 10 mg. of methyl testosterone at intervals varying from once in 2 weeks to 3 times weekly, with complete control of all the previously distressing symptoms.

Comment. The apparent disturbance of calcium metabolism seen at the first visit of this patient would appear to be more or less dissociated from the variations in gonadal function. The ability of the patient to decrease the dose of testosterone gradually without return of symptoms is nicely demonstrated.

Case 6, W.F.D., a 54-year-old male, first seen on Nov. 26, 1941, had for 3 or 4 years suffered from precordial pain radiating to both arms, brought on or aggravated by exercise and emotional stress and relieved by rest. Associated symptoms were long, sighing respirations, occasional nausea, mild headaches, tinnitus aurium, a dragging sensation in both hypogastric regions, sudden urge to void and slight burning on urination. Noteworthy findings on physical examination included a chronic granular pharyngitis, an emphysematous type of chest, a blood pressure of 162/96 mm. Hg, a pulse rate of 100 per minute, and a moderately hypertrophied prostate. The urine contained no abnormal constituents. The blood count was normal. The blood Wassermann reaction was negative. A roentgenogram of the heart and lungs confirmed the presence of a mild degree of hypertrophic pulmonary emphysema, but was otherwise normal. The basal metabolic rate was +8 per cent; no sighing respirations were seen in the tracing. Electrocardiograms were made before and after exercise. There was a normal sinus mechanism, a rate of 90 per minute, a moderate left-axis deviation, and low T-waves in *lead 1*, which were heightened by exercise.

He obtained no relief of symptoms from the use of aminophyllin suppositories or nitroglycerin tablets. Five injections of testosterone propionate, 25 mg. each, were given at 2-day intervals with disappearance of all the manifestations enumerated above. Following this, he used methyl testosterone, 10 mg. every other day, and 20 mg. on the alternate days for a period of 4 weeks. There was no recurrence of symptoms until 2 months later when methyl testosterone, 10 mg. daily, was again prescribed, with complete relief. The patient has utilized methyl testosterone intermittently to date (Nov. 1, 1942) with satisfactory control of all of the distressing symptoms.

Comment. The simultaneous relief of symptoms in several bodily systems, particularly in the cardiovascular and genito-urinary spheres, demonstrates rather unequivocally the specific nature of the condition and the treatment indicated for it. The urinary symptoms must not be confused with those of hypertrophy of the prostate. In observing 58 males with such manifestations of the climacterium, Douglas (9) has emphasized this point as well as the fact that relatively small total doses of hormone are required to relieve the distressing syndrome.

This and the cases yet to be described are illustrative of the long periods of relief which may follow even reasonably short periods of treatment.

Case 7, F.S., a 34-year-old male, suddenly developed sharp pain in the left lower chest anteriorly on April 3, 1941, which rapidly changed to a dull, constant ache. This pain radiated to his back between the shoulder blades and into the region of the left shoulder. The pain was associated with faintness and was aggravated by physical or mental activity. For several months prior to its onset he had noticed increased nervousness, easy tiring, heightened irritability and irascibility. He was a short, stocky, well-developed and nourished, firm-fibered individual. There was a marked right septal deviation, a chronic granular pharyngitis, and chronically inflamed tonsils. No organic heart disease was present; the pulse rate was 90 per minute; the blood pressure, 120/82 mm. Hg. Urinalysis, blood count, a teleroentgenogram of the chest, and an electrocardiogram failed to yield information of positive diagnostic value. Aminophyllin suppositories, 7.5 grains each, given twice daily, did not relieve the cardiac or other symptoms.

The patient was given testosterone propionate, 25 mg., by injection twice weekly for 6 weeks. His symptoms disappeared. Since that time he has had two implants of 300 mg. of testosterone (four 75-mg. pellets). The last of these was inserted on Jan. 19, 1942. Despite the fact that it should have been completely absorbed by April, 1942, the patient has had no return of symptoms to date (Nov. 1, 1942).

Comment. While the majority of males do not experience disturbances related to flagging testicular function until over 45 years of age, the possibility of hormonal imbalance must not be overlooked in the younger individual. This patient was a vigorous, active mental worker of unusually sedentary habits which may have contributed to the early appearance of the climacterium.

In the female, symptoms similar to those seen in the climacterium may be observed not infrequently in the period of adolescence. If we reason by analogy, it seems logical to expect such disturbances in some males at an equally early age. The problem is not necessarily one of primary gonadal deficiency, but rather one of hormonal imbalance, the exact factors of which are as yet poorly understood.

Case 8, H.C.I., a 40-year-old man, was first seen April 22, 1938, when he complained of insomnia, dizziness, 'sluggishness,' anorexia, constipation, persistent tiredness, occasional heartburn, and dull, dragging pain in the left lower chest, all of some 2 to 3 years' duration. The insomnia was described as a difficulty in getting to sleep. The dizziness was an outstanding symptom, at times so severe as to make him afraid to walk on the street alone. He had never been constipated prior to the onset of the present illness, but since then had used cathartics daily. His past history was irrelevant. He was accustomed to 4 to 6 scotch-and-sodas weekly; 4 to 5 cups of coffee daily, and half a package of cigarettes daily.

He was a well-developed, thin, highly nervous individual with a fine tremor of the hands, which were hot and perspired easily. There was no enlargement of the thyroid gland. The blood pressure was 108/80 mm. Hg; the pulse rate, 84 per minute. The basal metabolic rate was −21.5 per cent. The electrocardiographic tracing was normal except for a slight left-axis deviation.

The patient did not improve materially with the withdrawal of alcohol, coffee, and cigarettes, and the use of vasodilator drugs, mild sedation, vitamin B complex, and bile-salt therapy.

In February, 1940, he added impotence to his previous complaints, and stated that the dizziness, the precordial pain, and the insomnia were worse than when we had first seen him. Testosterone propionate in 25-mg. doses 3 times weekly relieved all of the complaints but the dizziness, which was improved, however. Such treatment was continued for 3 weeks, when the dosage interval was changed to twice weekly for 5 weeks. After that, therapy was given intermittently on indication until February, 1941, when a total of 625 mg. had been used. During this period his symptoms were reasonably well controlled. On Feb. 14, 1941, two pellets, each containing 75 mg. of testosterone, were implanted deeply in the subcutaneous tissues. Four such pellets were similarly placed on May 29, 1941. Following this treatment, there was no return of cardiac or other symptoms until July, 1942, since which time injections of 25 mg. of testosterone propionate at approximately semi-monthly intervals have made him reasonably comfortable.

Comment. This patient's cardiac symptoms were always mild and represented a rather minor incident in the clinical picture of his failing testicular function. The most striking feature was the return of sexual potency which has been well sustained since testosterone therapy was begun.

DISCUSSION

It is not difficult to see many points of similarity in the condition, clinical course, and response to treatment of these 8 patients. While it would have been desirable to make extensive studies of the excretion of various hormones, such determinations have not been particularly informative in the past (3, 4, 10, 11, 12). Efforts to estimate the amount of male hormone in the urine of human beings remains more a problem of the research laboratory than of the clinic.

Moreover, the relief obtained in these 8 cases by specifically directed treatment, when other measures had failed, seems to leave little room for doubt as to the origin of the symptoms. In fact, the complete disappearance of manifestations in the male climacterium is so prompt following testosterone therapy that this response may be used as a simple therapeutic test to differentiate complaints of this nature from those of other causation. In our experience, the pains of the arthritic, the distress of the individual with organic heart disease, and the urinary disturbances accompanying a true hypertrophy of the prostate have never responded rapidly and completely, if at all, to the administration of testosterone. We have never failed to relieve symptoms directly associated with the climacterium.

In retrospect, the clinical features by which we may recognize the cardiac syndrome in the male climacterium appear to be

1. Dull, constant oppression over and to the left of the sternum
2. A sense of uneasiness and insecurity throughout the chest
3. Attacks of angina-like pain, not necessarily related to effort and not relieved by nitroglycerin
4. Breathlessness totally unrelated to effort or to time of day or night
5. Long, sighing respirations, explained by the patient as an effort to relieve the sense of uneasiness in the chest
6. Paresthesias of various parts of the body, varying from a feeling of numbness to sharp, lightning-like pain, and distinguished from other types of pain by the fleeting nature and tendency to migrate rapidly from one part of the body to another
7. Palpitation or sense of palpitation without any change whatsoever in the heart rate
8. A depression of the S-T segment in all 3 limb leads of the electrocardiographic tracing
9. Associated symptoms suggesting the climacterium such as general mental and physical weakness, easy tiring; myalgic and arthralgic pains; digestive disturbances without evidence of disease in the gastrointestinal tract; mild urinary symptoms, including loss of force of urinary stream, terminal dribbling, and vague lower abdominal distress
10. Prompt relief of all symptoms, usually within 24 to 48 hours, following the parenteral administration of a testosterone preparation.

Emphasis should be placed upon the fact that, on the basis of the history and the physical findings alone, organic heart disease can not be eliminated as a diagnostic possibility in these and similar cases. If, however, precordial pain of other origin is strongly suggested, nitroglycerin and testosterone can be used as therapeutic tests as described above. A response to the former, with failure to react to the latter, eliminates the climacterium as the cause of the symptoms. Only a few years ago the patients described above would have been classified as cardiac neurotics and dismissed from the physician's office with sedation of one form or another. Today, under specific hormonal medication, they may pursue their daily round of activity without mental or physical handicap.

In applying testosterone therapy to the specific type of cardiac complaint which it is capable of relieving, it would seem to be of more than academic interest to make the distinction between the cardiac neurosis of the climacterium and an organic lesion. In the latter type of case, the increased libido quite commonly associated with the use of male-hormone therapy is highly undesirable and may be a factor in the production of a serious complication. Such may have been the case in one of Walker's patients (13), who obtained no relief from the hormone and after several weeks of treatment developed a coronary thrombosis.

A surprising feature of 3 of the cases above detailed (*H.C.M.*, *H.P.I.*, and *F.S.*) was the suddenness of onset, which was of such a character as to focus attention immediately upon the heart, and in one instance led to prolonged therapy for a possible disturbance in that organ.

Impotence was not a feature in 5 of the patients and was of slight degree in one of the 3 remaining individuals. It would appear that the climacterium is not simply a loss of the function of a single gland but a disturbance in the interrelationship of two or more glands. In keeping with this conception, Freeman found it possible to relieve impotence by the combined use of anterior pituitary-like hormone and testosterone, when neither alone was effective (14).

The mode of action of gonadal hormones upon the heart and circulation is not entirely clear. It has long been known that both estrogens and testosterone are vasodilating agents under certain conditions, and that testosterone

is a vasoconstricting agent in other circumstances. The phasic action of testosterone is of more than passing interest in this connection. We have observed aggravation of precordial pain from larger doses too frequently administered. Moreover, while an effect in lowering blood pressure is commonly observed, in our experience previously normal values have been elevated to hypertensive levels by the too vigorous use of the drug.

Perhaps the action of estrogens and androgens on the heart and circulation may be explained by a similarity in structure to the hormones of the adrenal cortex. Hormones from that structure have exhibited gonad-like effects (15, 16). Moreover, they are known to simulate some of the actions of the digitalis group of drugs, a fact probably related to the similarity between their respective chemical constitutions and that of the digitoxigenin fraction of the glucosides of digitalis (17).

The electrocardiographic changes which occasionally accompany the female climacterium (2, 5) have been demonstrated in one of 8 males. It is difficult to say under what conditions they may appear, particularly whether or not they are an index of the severity of the case. In *case 3* (*H.P.I.*) they developed while the patient was under observation, and not until his symptoms were sufficiently distressing to be completely disabling. Perhaps the other patients would have eventually developed such changes had treatment not been instituted earlier. It will take a large number of observations to throw real light on this problem.

The influence of testosterone propionate upon several varieties of angina pectoris has already been the subject of several reports (13, 18, 19, 20, 21). The implication of the majority of these is that testosterone therapy may be useful in any and all forms of the condition. Inasmuch as angina pectoris is a symptom of a wide variety of clinical conditions (22, 23) and not a disease entity, any appraisal of the relief afforded must, if possible, take into account the etiologic factor responsible for the pain.

The whole subject is one which does not lend itself readily to objective consideration. For example, in one of the three cases reported in detail by Walker (13), the electrocardiographic tracing was entirely normal 6 weeks prior to an infarction of the anterior wall of the heart, despite the fact that severe anginal symptoms had been present intermittently for at least 5 years. Testosterone therapy had afforded this patient no relief. Seven of 9 males observed by him were relieved under treatment with testosterone. One of those who did not improve developed myocardial infarction while receiving injections of the hormone. In none of Hamm's patients was there any alteration of the electrocardiogram from normal (21). Some of his patients obtained relief from attacks with the use of nitroglycerin, while all were relieved by the use of testosterone.

Bonnell and his associates (19) called attention to the beneficial effects of sex hormones in 23 patients with angina pectoris, 19 of whom had electrocardiographic evidence of myocardial damage; the character of the T-wave and QRS changes is not stated. Apparently, in the hands of these workers, estrogens and androgens were more or less interchangeable. Both were equally capable of improving the condition of patients who had had and those who had not had coronary occlusions. Six patients were completely relieved, whereas 11 continued to have modified attacks while still under treatment. Walker has improved the condition of patients with anginal syndromes and those with paroxysmal nocturnal dyspnea (18). His conclusions are very conservatively stated and include caution against the excessive use of the material, particularly in the elderly. One gains the impression that he looks upon the action of the male and female sex hormones in relieving pain in the chest as far more than a simple, direct effect upon the vascular tree. Our own experience would be in entire accord with such an opinion.

In his own studies and in the literature quoted by him, Lesser (20) emphasized the vasodilating effect of testosterone. All 24 of his patients obtained varying degrees of relief lasting for from 2 to 12 months after treatment was discontinued. In each of his patients, attacks were 'quickly relieved by rest or nitroglycerine.' Electrocardiographic studies were not mentioned.

One fact stands out clearly in the reports of all observers, *viz.*, that no direct relationship exists between the severity of the precordial

pain, the degree of demonstrable cardiac damage, and the relief to be obtained from sex-hormone therapy. Such a conclusion should lead us to suspect that the action of testosterone is not a simple, direct and non-specific pharmacologic action upon the vascular tree, but an indirect effect, probably mediated through a variety of metabolic changes. Neither the biochemist nor the clinician is entirely lacking in evidence to substantiate such a viewpoint. Not all patients with precordial pain have been relieved. The degree of relief has borne no recognizable relationship to the degree of demonstrable coronary sclerosis. The action of the hormone has not been predictable on the basis of previous responses to the usual vasodilators. On the contrary, many cases totally refractory to vasodilator drugs have been completely relieved by testosterone (our own cases and 13, 18, 19). The action of the vasodilator drugs can usually be detected in from several minutes to 2 to 3 hours; that of testosterone, in not less than several hours.

Certain metabolic effects of a general character may play a more than cursory rôle in the action of testosterone upon the circulation: *a*) The hormone has been shown to decrease the renal excretion of inorganic phosphorus, total nitrogen, sodium, chloride, and water (7, 24, 25, 26, 27, 28, 29), although its action on sodium, chloride, and water retention is feeble as compared with that of the estrogens and certain steroids of the adrenal cortex (24). *b*) Testosterone propionate has increased the excretion of potassium (30). *c*) After castration, the amount of creatine phosphate and glycogen in the heart of the rat decreased to about two-thirds normal (24). These values were returned to normal and above by the administration of testosterone (24). *d*) Testosterone given to normal rats increased the glycogen content of the heart by as much as 100 per cent (24). *e*) The metabolic rate in human beings with testicular deficiency has been increased by testosterone (7, 8).

The above facts justify the conclusion that the cardiac symptoms of the male climacterium represent a specific type of precordial distress for which gonadal-hormone therapy is the most satisfactory treatment. While such a conception does not preclude the possibility of utilizing testosterone in the management of a wide variety of anginal syndromes, too much must not be expected of the drug in the absence of other symptoms of the climacterium.

SUMMARY

Severe angina-like pain was observed in 8 patients which did not respond to treatment with vasodilator drugs and sedatives, but was promptly relieved by the administration of testosterone. When looked for, other evidence of changing testicular function was present, such as impotence, easy tiring, myalgic and arthralgic pains, vague digestive complaints, mild genito-urinary symptoms, insomnia and vasomotor disturbances. As a group, these patients represent a syndrome in which some cardiovascular disturbance, notably precordial pain, is the predominant expression of the male climacterium. Their failure to respond to the usual vasodilator drugs distinguishes them from other forms of angina pectoris which may or may not be relieved by sex-hormone therapy. The influence of testicular hormones on cardiac activity is briefly discussed.

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Influence of the Menstrual Cycle on the Titer of Circulating Allergins

O. C. HANSEN-PRUSS, M.D.
AND RUTH RAYMOND

From the Division of Allergy, Medical Department, Duke University, Durham, North Carolina

IT HAS BEEN suggested frequently that the menstrual cycle influences the occurrence and severity of allergic phenomena. Many clinical observations seem to bear this out, yet experimental studies are lacking. The assumption that 'a state of hypersensitiveness is frequently observed in the premenstrual period and the early days of menstruation' (1) is based on clinical impressions rather than on concrete evidence.

In a recent paper (2) we reported that the reactivity of the female skin to test allergins was the greatest during the last day of catamenia. It was pointed out that this did not imply an increase in hypersensitiveness in allergic individuals. It was suggested that the larger spread of the test allergins in the skin was due to relative dehydration in the late menstrual phase and that it coincided with the period of estrogenic deprivation.

To determine whether or not the allergic state is influenced by the menstrual cycle the following studies were made. Four young females (age range 19 to 23 yr.), who were hay fever sufferers, were chosen. All were found to give strong positive skin reactions to the intradermal injection of various test substances. They were skin tested 10, 4 and one day before menstruation, on the last day of catamenia, and 4 and 10 days after cessation of menstruation. Venous blood for passive transfer tests was obtained each time before the skin tests were made. The test substances were *a*) short ragweed (dilution 1:1000), *b*) dust (dilution 1:1000), *c*) staphylococcus toxoid (dilution 1:1000), *d*) monilia albicans (dilution 1:100) and *e*) wheat (dilution 1:100).

Since short ragweed produced the strongest skin reaction in every subject, this was chosen as the test substance for the passive transfer tests. These passive transfer tests were made on 5 male medical students (age range 20 to 22 yr.) who gave a negative personal and family history for allergy. They had been skin tested with the common test allergins and did not give positive reactions to the intradermal injections of these substances. The prepared serum obtained from the allergic women was injected intradermally on the dorsal surface of the trunk of the male students. As a rule .05 cc. of the various sera was used to sensitize the local areas. Twenty-four hours later 0.1 cc. of test substance, short ragweed in a dilution of 1:1000, was injected into each prepared site. The reactions were read in 20 minutes and the size was determined accurately with a planimeter and recorded in sq. cm. It was found in every instance that the wheal was about 2 sq. cm. and was surrounded by a zone of intensive erythema of variable width. The outer margin of intense erythema was considered to represent the maximum size of the reaction and this was the area measured with the planimeter.

The outcome of the passive transfer tests is given in tables 1 to 4.

It will be seen that the greatest skin reac-

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TABLE 1. PASSIVE TRANSFER TESTS IN MALES USING SERA FROM FEMALE *1*, SENSITIVE TO RAGWEED

Time of cycle with reference to onset of menstruation	Days before Catamenia		Catamenia		Days after cessation of Catamenia	
	10	4	1	last day	4	10
Size of reaction, (sq. cm.) Female	2.64	7.41	5.15	7.80	7.61	6.45
Passive transfer tests; blood serum obtained on corresponding dates						
Male 1	2.9	5.8	7.24	8.84	6.45	7.16
Male 2	6.9	9.68	8.96	7.75	9.23	4.58
Male 3	5.03	7.29	9.68	12.13	9.68	6.65
Male 4	0.64	1.94	4.38	3.55	3.48	0[1]
Male 5	1.42	1.35	2.71	6.32	0[1]	2.13
Average size reactions, sq. cm.	3.57	5.20	6.59	7.71	5.80	4.10

[1] checked twice.

tions were obtained in sites passively sensitized with the serum withdrawn on the last day of menstruation. The smallest reactions occurred using sera obtained on the 10th day following cessation of menstruation. A few exceptions were instances in which the least reaction occurred in sites prepared with serum from samples obtained on the 4th day after cessation of menstruation. In one group of experiments the smallest reactions were found in sites sensitized with blood withdrawn on the 10th day preceding the onset of menstruation.

DISCUSSION

The passive sensitization of skin sites in nonallergic individuals was made by the Prausnitz-Kustner technic. Since it has been shown that the passively acquired reaction is due to the interaction of sensitizing bodies and the test allergin, the positive reaction is indicative of the presence of such specific reagins. Furthermore, the size of the reaction is determined by the strength and quantity of the reagin. In our experiments the test sera were all collected and tested in a similar fashion, and the amount injected into the skin was always 0.05 cc. The test allergin was in every instance the same. We can deduce, therefore, that the size of the reaction is indicative of the titer of circulating allergins. The average size of the reaction is summarized in table 5.

It is seen that sera collected during the last day of menstruation have the highest allergin titer. The lowest allergin titer was found in sera collected on the 10th day before the onset of catamenia. Relatively low titers were found

TABLE 2. PASSIVE TRANSFER TESTS IN MALES USING SERA FROM FEMALE *2*, SENSITIVE TO RAGWEED

Time of cycle with reference to onset of menstruation	Days before Catamenia		Catamenia		Days after cessation of Catamenia	
	10	4	1	last day	4	10
Size of reaction (sq. cm.) Female 2	11.45	15.16	15.48	18.71	16.38	14.46
Passive transfer tests; blood serum obtained on corresponding dates						
Male 1	18.32	13.87	17.87	22.32	20.86	21.64
Male 2	11.16	12.38	12.64	15.50	12.52	13.47
Male 3	14.89	13.52	15.92	18.98	16.22	11.16
Male 4	8.51	9.30	10.31	13.35	12.74	8.06
Male 5	10.00	14.21	14.35	15.59	13.82	11.87
Average size reactions, sq. cm.	12.57	12.25	14.21	17.14	15.23	13.20

TABLE 3. PASSIVE TRANSFER TESTS IN MALES USING SERA FROM FEMALE *3*, SENSITIVE TO RAGWEED

Time of cycle with reference to onset of menstruation	Days before Catamenia		Catamenia		Days after cessation of Catamenia	
	10	4	1	last day	4	10
Size of reaction (sq. cm.) Female 3	13.89	12.80	12.3	16.96	15.38	13.48
Passive transfer tests; blood serum obtained on corresponding dates						
Male 1	2.25	16.74	17.09	23.05	16.15	17.77
Male 2	10.45	11.67	12.85	15.74	14.16	9.42
Male 3	10.98	10.05	15.03	17.04	14.83	11.72
Male 4	8.06	9.42	8.25	10.42	9.09	6.65
Male 5	11.10	14.96	14.16	16.22	13.93	10.90
Average size reactions, sq. cm.	8.44	12.56	13.47	16.59	13.63	11.29

TABLE 4. PASSIVE TRANSFER TESTS IN MALES USING SERA FROM FEMALE *4*, SENSITIVE TO RAGWEED

Time of cycle with reference to onset of menstruation	Days before Catamenia		Catamenia		Days after cessation of Catamenia	
	10	4	1	last day	4	10
Size of reaction (sq. cm.) Female 4	9.95	2.35	9.23	15.48	14.38	10.45
Passive transfer tests; blood serum obtained on corresponding dates						
Male 1	15.25	17.48	18.21	24.35	2.06	21.18
Male 2	12.70	12.92	14.64	19.77	18.12	14.83
Male 3	13.20	16.12	13.09	18.77	15.89	13.93
Male 4	6.65	8.19	8.20	10.82	8.45	7.29
Male 5	11.60	10.23	13.42	15.21	14.89	9.74
Average size reaction, sq. cm.	11.88	12.98	13.51	17.78	11.88	13.39

TABLE 5. AVERAGE SIZE OF SKIN REACTIONS OBTAINED BY PASSIVE TRANSFER TESTS

Time of cycle with reference to onset of menstruation	Days before Catamenia		Catamenia		Days after cessation of Catamenia	
	10	4	1	last day	4	10
(sq. cm.)	9.11	10.74	11.99	14.80	11.63	10.49

also in sera obtained on the 4th day before and the 10th day after catamenia. Roughly, the low titers correspond to estrogenic peaks. The highest allergin titer was found in the sera obtained on the last day of menstruation which marks the end period of estrogenic deprivation (3). These observations suggest, therefore, that the allergin titer in the sera of allergic females is inversely proportional to the estrogenic level. Furthermore, the highest serum allergin titer is found at that time of the menstrual cycle at which the reactivity of the female skin is greatest (2).

SUMMARY AND CONCLUSIONS

Serum from allergic women was used for passive transfer tests. The sera were collected in the mid-period of the menstrual cycle, 4 days before catamenia, on the first and last day of menstruation and 4 days after cessation of the menses. Tests were made through at least one complete cycle. The subjects chosen for the

passive transfer tests were 5 healthy, proven non-allergic male medical students. The passive transfer was made according to the Prausnitz-Kustner technic. Since all 4 females were clinically sensitive to short ragweed, and gave a very strong positive skin reaction to short ragweed allergin, this was used as the test substance. The reactions were measured with a planimeter and were recorded in sq. cm. The largest positive reactions were observed in sites sensitized with sera obtained on the last day of menstruation. The smallest reaction was seen in areas which had been prepared with the sera obtained 10 days before the onset of menstruation.

It is concluded that the serum of allergic women contains the highest allergin titer on the last day of menstruation, a period which marks the end phase of estrogenic deprivation. Furthermore, the results obtained show that the highest serum allergin titer is found when the skin of women is most reactive. It is therefore suggested that the serum allergin titer of allergic women is in inverse proportion to the estrogenic level.

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The Treatment of Obesity[1]

WINDSOR C. CUTTING, M.D.

From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, California

THAT OBESITY is common in a land of plenty is not surprising, but that obesity is prevalent among the financially poor seems paradoxical. Impoverished patients nearly all complain that they cannot afford to eat a reducing diet. They find it almost impossible to restrict cheap and accessible foods like bread and beans to the small portions which will allow them to lose weight. The foods with less caloric value, like vegetables, fruits, and meats, they find too expensive, although these might give the desired satisfaction of appetite, if eaten.

Obviously, all obesity is due directly to eating more food than the body needs for maintenance and operation. The excess is stored as fat, very little being wasted in stools (1). Why is it that some persons find it difficult not to eat more than they need? Why do some get fat on an amount of food which would cause others to lose weight? The second question is the easier, and may be answered simply by saying that the natural energy requirements of those who eat small amounts are less because of less, or more efficient, activity, and a more phlegmatic temperament. These energy requirements relate to their 'working' metabolism; very few have a truly decreased 'basal' metabolism. Obesity is not particularly characteristic of hypofunction of the thyroid or other endocrine glands.

The first question is much more profound, and not entirely answerable at present. Some believe that the obese overeat because of gluttony (2), others that their tissues have a tremendous affinity for fat (3), storing it whenever possible, and relinquishing it only when strongly forced. It is difficult to reconcile the second view with the demonstration that the fat in cells is metabolically active (4) and with the fact that, unless an excess of food were eaten, the body would lack in energy requirement because of the loss of food material to fat depots. The first belief, however, has 'moral' implications which many are unwilling to grant. Certainly the girl disappointed in love may take to candy, or a mother may teach her child to stuff himself, but no such obvious cause is present in women who gain weight after the birth of children, or, for that matter, in most obese persons. At the moment one cannot say whether these normal obese persons have some psychologic drive which requires satiation by eating, or whether the natural regulation of appetite, which presumably is centered in the base of the brain, is one of an abnormally high level—through hereditary acquisition, or as a result of encephalitis, tumor, or other disease affecting this region. In the normal person, at least, appetite is satisfied at a point where nourishment is adequate; in an obese person, appetite is not yet satisfied at this point.

Experimentally, in mice with hereditary obesity, both activity and appetite seem to be at abnormal levels, conducive to obesity (5). In human beings it is difficult to determine the relative importance of the two factors, and it may be assumed that both are probably present, but that, in any event, the appetite dictates that more be eaten than the person needs.

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TABLE 1. REDUCING DIET DESIGNED TO ALLOW CONSIDERABLE VARIATION IN MENUS

Reducing Diet: 960 Calories

Carbohydrate, 80 gm.; Protein, 70 gm.; Fat, 40 gm.

Breakfast	
Fruit	1 serving
Cereal	1 tablespoon (dry measure before cooking)
Bread	1 slice
Egg	1
Skim milk	1 standard measuring cup (or canned milk ¼ cup)
Lunch	
Lean meat, fish or fowl	1 small serving
or cheese	1 small slice
or cottage cheese	2 heaping tablespoons
or eggs	2
Vegetables	2 generous servings (2 cups)
Skim milk	1 standard measuring cup (or 1 cup buttermilk)
Fruit	1 serving
Supper	
Lean meat, fish or fowl	1 medium serving (¼ pound)
or cheese	2 oz. (⅛ pound)
Vegetables	2 generous servings
Fruit	1 serving

One serving of fruit: 1 grapefruit; 1 orange; 1 cup berries; ¼ slice watermelon (across); ½ small cantaloupe; 1 pear; 1 peach; 3 apricots; 2 plums; 1 small apple; 1 small banana; ½ cup orange juice; ½ cup pineapple juice; 1 cup tomato juice; 1 cup grapefruit juice; ⅓ cup dried stewed apricots; ⅓ cup dried stewed prunes (stewed without sugar).

Patient may take: Clear soup, plain tea or coffee with any meal. Saccharin (¼ grain) may be used for sweetening, if desired. Liquid petrolatum (mineral oil) may be used to replace fats and oils, as in salad dressing.

Vitamin capsules (polyvalent) daily as prescribed (usually 2).

Patient should avoid: Bread in any form, except as stated above, including gluten bread, melba toast, crackers, Rye Krisp and advertised 'reducing breads.'

Starchy foods: rice, noodles, potatoes, beans, corn, peas.

Sweets: honey, jam, sugar, candy and all desserts.

Sweet fruits: prunes, grapes, persimmons, cherries, figs, and all fruits canned with sugar.

Fats: gravy, salad dressing, mayonnaise, oil, cream, butter, lard, avocado.

Treatment

Treatment of obesity at present is based on one, or both, of two rational procedures, *i.e.*, to reduce the food intake, or to increase the activity. Because almost any adult, no matter how small, or how inactive, requires at least 1500 calories daily, it is obvious that a diet restricted to 1000 calories will make him lose weight. Since a reduction program usually lasts many months, such a diet must be designed to be adequate in protein, minerals, and vitamins. Table 1 shows a diet, of about 1000 calories, which is used more or less routinely in the Stanford Endocrine Clinic. A polyvitamin supplement, including especially the B complex, is given in addition. Some patients easily follow such dietary advice, and others may be cajoled or threatened into doing so. Cosmetic arguments are often most telling, but the greater likelihood of diabetes and possible osteoarthritis and hypertension, as well as undoubtedly greater fatigue, also may be stressed. Ideally, about two pounds a week should be lost.

As an adjunct to diet, greater activity is sometimes possible. Often, however, the pleasure and increased feeling of well-being after exercise are mirrored in a correspondingly increased appetite. Dinitrophenol and thyroid cause the equivalent of increased activity, and have been used for this purpose. Because of possible toxic side-effects, dinitrophenol should not be used, and may not be prescribed in California. On the other hand, thyroid in moderate

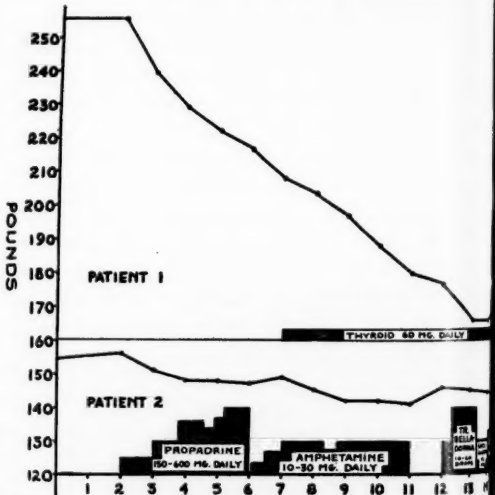

FIG. 1. (*Upper curve.*) Chart of patient who lost weight successfully on regimen of diet, later with the adjunct of small doses of thyroid. Note failure of this agent to influence the slope of the curve. (*Lower curve.*) Chart of patient who failed to lose weight satisfactorily on dietary restriction plus propadrine, benzedrine, belladonna, saccharin and sodium phosphate.

doses (0.06 to 0.18 gm.; 1 to 3 grains), may cause relatively little discomfort from sweating, tachycardia and fatigue, and so is frequently used. Because dietary restriction is much more effective than thyroid administration in safe doses, thyroid is seldom given at the onset of treatment, in order to emphasize the necessity of diet. Later, however, especially if the patient has reached a plateau in body weight, below which it is difficult to go, thyroid may tip the balance, and allow further loss of weight. Figure 1 (upper curve) is typical of results in the patients who lose weight adequately on the above regimen. It should be added that some experienced endocrinologists regard the addition of thyroid as completely futile—as it it obviously was in this case.

Many patients, possibly the majority, fail to lose weight over any considerable period by the measures just discussed. This is because of lack of drive, or will power, to follow the diet more than a month or two. All obese persons are poor candidates for reduction, as indicated by the fact that they have allowed themselves to become fat. It is not surprising that many backslide on their promises. Therefore, since dietary limitation appears to be more important than increased activity for most patients, much attention has been given to means for decreasing the appetite, or disturbing the absorption of food, by medicinal agents, rather than persuasion. Several agents have been reported to be efficacious, but most reports include patients who might have done well on diet alone. For this reason, stubborn losers, who had apparently tried their best to follow the diet, but who had failed to do so, as indicated by failure to lose weight over a period of several months, were selected for trial of various allegedly effective agents. According to the results to be described, they also failed to lose weight even with these aids to decrease their food intake.

Propadrine hydrochloride. Because amphetamine sulfate has been claimed to cause loss of body weight, both experimentally (6) and clinically (7, 8) (the mechanism of action not being clear) it was decided to try the effect of propadrine,[2] a related sympathomimetic amine, at the suggestion of Professor M. L. Tainter, of the department. Propadrine was tried first, because it causes relatively minor stimulation. Fifteen trials were made on the 13 patients, with doses starting at 25 mg. (3/8 grain) three times a day, one-half hour before meals, and increasing to 50 mg. (3/4 grain) every hour while awake. The average loss of weight was 5 pounds in an average of 10 weeks of trial, or a loss of only one-half pound a week, which was decidedly unsatisfactory. Only one patient had what might be considered an adequate response, *i.e.*, a loss of 21 pounds in 27 weeks. With one exception, the patients had no complaints referable to the medication; only one patient complained of tachycardia and abdominal discomfort. Specifically, no nervousness, dry mouth, thirst, insomnia, visual disturbances, or sweating were reported. On pointed questioning, a few admitted some loss of appetite. There was no significant change in blood pressure at any time.

Amphetamine sulfate. Six patients were given amphetamine in doses of 10 to 30 mg. daily, the drug being given during the morning. In an average period of 13 weeks, they lost an average of 4 pounds, or about one-third of a pound a week. Only one patient showed an adequate weight loss, *i.e.*, 24 pounds in 12 weeks. Two of the 6 patients complained of insomnia and breathlessness; one of tachycardia in addition.

Miscellaneous. Tincture of belladonna has been reported to increase weight loss (9), possibly by drying the mouth, thus making the food unpalatable. Five patients, given 10 to 20 drops of the tincture one-half hour before meals failed to lose any weight in one month's time. Two were given 16 mg. (1/4 grain) of saccharin before meals, but this also did not interfere with their eating, and no weight was lost in one month's time. One patient, on her own decision, took 8 gm. (2 drams) of sodium phosphate every morning for one month, losing no weight. This agent presumably owes any action to the catharsis produced. Figure 1 (lower curve) shows the negative results of the efforts of this patient to reduce. She was obese, although not so fat as *patient 1* who was taller; the two curves are not exactly comparable. It often seems easier for persons grossly overweight to follow

[2] The propadrine hydrochloride used was supplied by Sharpe and Dohme, Philadelphia, Pa.

a strict regimen than those only moderately overweight.

SUMMARY

Many obese patients may be helped to lose weight by advice as to a reducing diet, possibly with the addition of small doses of thyroid (U.S.P.) at certain times. Many others fail to lose on such a regimen, which suggests that they are unable to restrict themselves to the prescribed food, due to the drive of appetite. These latter unfortunates are also resistant to various medicinal agents, which have been often recommended for decreasing the appetite. Probably amphetamine sulfate and propadrine aid in reducing only those who can also bring themselves to restrict their diet, thus denying the allegedly intrinsic value of these agents in the treatment of obesity.

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The Oral Effectiveness of Estrone Sulfate (Conjugated Estrogens-Equine) in Women

S. C. FREED, M.D., W. M. EISIN, M.D. AND J. P. GREENHILL, M.D.

From the Endocrine-Gynecology Clinic, Mercy Hospital, and Loyola University School of Medicine, Chicago, Illinois

THE IMPORTANCE of assaying estrogens directly in the human female for the purpose of therapeutic standardization has been emphasized repeatedly (1,2,3). Such a procedure would eliminate to a considerable extent errors resulting from the acceptance of biologic assays of estrogens for clinical purposes. We have already assayed in the human female the synthetic estrogens, diethylstilbestrol, hexestrol (2) and octoffolin (3) when administered orally. We have now extended our work to the assay of the natural estrogen, estrone sulfate.[1] For such assays we have used as the criterion of potency the subjective response of menopausal patients as described in previous reports. With this method we have employed multiple dosage levels of estrogens and have taken certain precautions aimed at eliminating a number of nonspecific factors which might influence the interpretation of results. These precautions include the omission of suggestion, the use of only those patients who have moderate or severe symptoms, the evaluation of relief of all patients by one of us and the changing of dosage levels without informing the patient.

Estrone sulfate is a naturally occurring estrogen found in the urine of pregnant mares. It is a water-soluble substance and, according to the available laboratory evidence, it is several times more potent than free estrone by mouth when administered to spayed rats.

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[1] The estrone sulfate (Premarin) was supplied by Ayerst, McKenna and Harrison, Rouses Point, N. Y. This preparation is a complex of estrogens occurring in pregnant mare's urine in which estrone sulfate predominates. It is assayed in terms of that substance.

METHODS AND RESULTS

Estrone sulfate was administered in three dosage levels: 1.25 mg., 0.81 mg. and 0.4 mg., three times a day in tablet form. The patients who were selected for use in testing the potency of this substance complained of moderate or severe symptoms including at least two hot flashes daily as well as other typical symptoms of the menopause such as nervousness, and dizziness. The patients usually received the highest dosage level at the beginning of treatment. After two weeks of such therapy the relief of symptoms was evaluated and tabulated as follows: 3+, complete relief; 2+, satisfactory; 1+, slight; 0, no relief. The patients were then given the substance in the next lower dosage level and after two or three weeks the symptoms were evaluated; after a similar period of treatment on the lowest dosage level the symptoms were again evaluated. The following table contains data on our results with the use of estrone sulfate orally.

TABLE 1. EFFECT OF DIFFERENT DOSAGES OF ESTRONE SULFATE ON MENOPAUSAL SYMPTOMS

No. Cases	Dosage mg. t. i. d.	% Responding			
		0	1+	2+	3+
45	0.40	11	6	57	26
47	0.81	8	12	42	38
60	1.20	4	10	43	43

From the data in table 1 it is seen that at the lowest dosage level the majority of patients obtained satisfactory relief from their symptoms. At the higher dosage levels there appeared to be no significant increase in the relative number of patients who obtained definite relief but a greater proportion of patients had complete relief. The lowest level, however, may be considered adequate for therapeutic purposes for the average patient. The possibility exists, of course, that even smaller amounts of this substance might be satisfactory for a significant number of cases. The incidence of side reactions with estrone sulfate is very low at the lowest dosage level since only one patient complained of nausea; at the middle dosage level 2 patients developed nausea and 2 complained of dizziness; and at the highest dosage level 5 patients developed nausea and 4 complained of dizziness.

TABLE 2. EFFECT OF DIETHYLSTILBESTROL ORALLY ON MENOPAUSAL SYMPTOMS

No. Cases	Dosage mg. t. i. d.	% Responding			
		0	1+	2+	3+
53	0.5	17	32	34	17
65	1.0	9	15	41	35

Uterine bleeding was noted in a number of patients. This occurred with one patient who was receiving the highest dosage level; two patients, the middle dosage level; and five patients the lowest dosage level. From these scanty data one might consider that the threshold dosage for uterine bleeding would be between the middle and lowest dosage level since the greatest number of patients showed uterine bleeding when the dosage was stepped down from the middle to the lowest level.

When the potency of this substance is compared to that of diethylstilbestrol a very interesting relationship may be observed. Table 2 contains data on the relief of patients who received 0.5 mg. and 1.0 mg. of diethylstilbestrol administered daily in a manner quite similar to that of estrone sulfate.

It will be observed that results with the lowest dosage level of estrone sulfate (1.2 mg. daily) are definitely superior to those with 0.5 mg. daily of diethylstilbestrol, although 1.2 mg. of estrone sulfate was not as effective as 1.0 mg. of diethylstilbestrol daily. At the dosage level of 2.4 mg. daily estrone sulfate is slightly superior to 1.0 mg. daily of diethylstilbestrol. It is acknowledged, however, that this comparison may have been affected somewhat by the administration of estrone sulfate in 3 doses during the day while diethylstilbestrol was administered once daily.

DISCUSSION

The average therapeutic dose of estrone sulfate is approximately 1.2 mg. daily when administered by mouth in 3 divided doses. Inasmuch as a portion of this substance is in the form of an inactive sulfate radical, the actual amount of estrone involved is approximately 0.9 mg. daily. Since this amount is more effective than the dose of 0.5 mg. of diethylstilbestrol daily, but less effective than 1.0 mg. daily, and since 1.8 mg. of estrone is slightly superior to 1.0 mg. of diethylstilbestrol, our results would, therefore, indicate that the ratio of oral effectiveness of estrone in the form of estrone sulfate to diethylstilbestrol is no less and possibly greater than 1:2. It is thus apparent that the loss of activity of orally administered estrone in the form of estrone sulfate is no greater than that of diethylstilbestrol, since the latter compound is, according to considerable evidence, two or more times as potent as estrone by injection. It is interesting that Stoddard and Metzger (4) have shown that 1.0 mg. of estrone by injection is equivalent to 0.5 mg. of diethylstilbestrol by mouth on the basis of vaginal smear reactions. As a matter of fact, comparison of our results with those of the above workers would indicate that estrone in the form of estrone sulfate is about as effective by mouth as estrone by injection since 0.9 mg. of estrone in the form of estrone sulfate is at least as effective as 0.5 mg. of diethylstilbestrol by mouth. We are unable to signify whether estrone in the conjugated form is more or less effective than free estrone when administered by mouth or, in other words, whether free estrone is equally as resistant to destruction under these conditions. While no definite conclusions can be made at the present time it would appear from our results that estrone sulfate possesses nearly as great a potency by mouth as estrone by injection. In as-

much as considerable evidence is available that most of the estrone administered orally to laboratory animals is destroyed, the unreliability of utilizing laboratory assay methods for therapeutic standardization is quite apparent.

In regard to toxicity, there are a few untoward reactions when estrone sulfate is administered in the average therapeutic dose of 1.2 mg. in three divided doses daily. Such therapy would, therefore, possess definite advantage over the administration of an equally effective therapeutic dose of diethylstilbestrol where the incidence of toxicity is 10 to 20 per cent. It is possible that one of the factors contributing to the low incidence of toxic reactions observed with estrone sulfate is due to the use of the divided dose technic since this would allow for a more uniform rate of absorption of the estrogen and a lower level of blood estrogen. This would be in accordance with the theory of estrogen toxicity postulated by us which is that toxic reactions are due to rapid absorption of estrogen with resulting high levels in the blood (3).

We have attempted to determine whether or not there was a greater sense of well-being in those patients who received estrone sulfate than in those who received comparable therapeutic amounts of diethylstilbestrol. While such data are rather difficult to obtain because of the subjective nature of the evidence, it is our impression that a significant number of patients preferred the natural estrogen to diethylstilbestrol because of a greater sense of general relief, exclusive of the amelioration of hot flashes. This possibly may have been due to the fact that the synthetic estrogen might induce in some patients a low grade toxic effect which was not sufficient to give the full-blown symptoms of toxicity such as nausea, dizziness and headache, but was manifested by a failure to obtain a feeling of relaxation and general relief.

SUMMARY

Estrone sulfate was administered to a group of women with well marked symptoms of the menopause. Optimal results were obtained with 1.2 mg. daily in three divided doses while 0.4 mg. three times daily induced satisfactory relief in most patients. It is relatively non-toxic in the average therapeutic dose. In the human female relatively little of the estrogenic activity of estrone sulfate is lost through oral administration, a finding which is contrary to results obtained in laboratory animals.

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Clinical Study of A New Type of Estrogenic Preparation for Oral Use

LAMAN A. GRAY, M.D.

From the Department of Obstetrics and Gynecology, University of Louisville Medical School, Louisville, Kentucky

THE CLINICAL effectiveness of natural estrogens when they are administered orally for the treatment of women, particularly in the menopause, has for many years been a controversial subject. Although subjective improvement has been frequently reported it has been difficult to demonstrate objective indications of the value of most of them. For a time it was felt that diethylstilbestrol might solve some of the problems of oral estrogenic therapy. There is no doubt that it will produce tissue changes. In fact, from a laboratory point of view, one can do with it anything that can be expected of natural estrogens. However, clinical experience reveals that there are a considerable number of women who do not tolerate diethylstilbestrol well and who do not seem to obtain from it the feeling of well-being that is often observed with the administration of natural estrogenic substances. In addition, there are many workers who are not satisfied that it will be as safe to use over extended periods of time as are natural estrogens. Thus there is a need for a potent estrogenic substance from natural sources that will be definitely effective when administered by mouth, if for no other reason than to treat individuals who do not respond well to the synthetic drug.

Recently a new type of natural estrogenic preparation has appeared on the market. This product consists of the natural conjugated estrogens of pregnant mares' urine.[1] The predominating estrogen is estrone sulfate and the product is standardized in terms of milligrams of conjugated estrogens expressed as estrone sulfate. Laboratory data indicate that this material is much more effective when administered by mouth than any estrogenic preparation from this source heretofore used. It is the purpose of this paper to report a clinical investigation of this new estrogen.

Type of patient studied. Clinical studies with this new conjugated estrogen have been made on 64 women in the menopause. Menopausal symptoms were present in 62 of these; 2 had no symptoms but did show vaginal changes. The symptoms when present consisted chiefly of hot flashes. However, nervousness, excitability, sleeplessness, gastro-intestinal complaints and arthralgia were observed in varying degree in a considerable number of patients. Fifteen of the 64 were graded as having symptoms of a degree of 4+; 32, 3 plus; 13, 2 plus and 2, 1 plus. Vaginal atrophy was studied in 63 cases and the atrophy was graded from 1 to 4 by studying vaginal smears. Thirty-two were classified as *grade 4;* 18, *grade 3;* 5, *grade 2* and 7, *grade 1.* One case showed no vaginal atrophy but did have menopausal symptoms.

Result of treatment. The result of treatment was gauged on the basis of symptomatic im-

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[1] The preparation is known commercially as Premarin and is manufactured by Ayerst, McKenna and Harrison Ltd., Rouses Point, N. Y.

provement and changes in the vaginal smear. Improvement in symptoms was considered complete or very marked in 46 of the 64 patients studied. Eight showed moderate improvement, 4 of whom had only 2 plus symptoms and 2 had *grade 1* epithelial atrophy. One patient had severe arthritis and another had been treated with radium; in these it was difficult to judge the result of treatment. Three patients had slight improvement; one of these had no epithelial atrophy and one had *grade 1* epithelial atrophy. In the remaining 7 cases sufficiently accurate data for estimation of the results of treatment were not obtained.

Restoration of normal vaginal epithelial structure was considered complete in 45 cases. This was accompanied by a smear characteristic of the follicular phase. In 4 patients the smears showed only moderate changes toward a follicular phase, but smears from 2 of these could not be made until after administration of the hormone had been discontinued for 10 days. The smears from the other 2 showed definite changes toward a follicular phase but were not fully cornified. The remaining 15 patients did not have vaginal examinations or smears made following treatment.

In general, symptomatic improvement was striking within 7 to 14 days after treatment was begun. Three patients who had taken diethylstilbestrol felt that they had a greater feeling of well-being when taking the conjugated estrogen. One patient noted especially a mental improvement, in contrast to the result obtained with the diethylstilbestrol previously used. Four patients felt there was an improvement in emotional balance when taking this oral estrogen, in comparison with the result of previous administrations of estradiol benzoate or estrone by injection. While parenteral therapy had been of tremendous value, all 4 of these patients were particularly concerned with the gradual let-down occurring 4 to 7 days after injection. One patient, with severe symptoms, including arthralgia, was treated for 2 years by parenteral administration of 1 mg. of estradiol benzoate every 2 to 6 days. This was associated with marked improvement. The vaginal smear at the end of that time showed a full follicular phase, although the vaginal secretions were scant and the rugae were unusually small. Even more complete substitution was obtained with the conjugated natural estrogen given in a single dose of 1.25 mg. orally per day. The vagina developed marked rugae and mucous secretion; cast-off squamous cells became much more numerous.

Dosage. Usually a complete growth effect and a vaginal smear characteristic of the full follicular phase develops in the *grade 4* atrophic vagina when 1.25 mg. is given daily for 7 days. In our experience this growth effect is equivalent, mg. for mg., with that produced by diethylstilbestrol when it is given by mouth, if indeed it is not somewhat stronger. In certain cases, specially prepared capsules containing 0.62 mg. and 0.31 mg., respectively, have been used. The former dosage will usually produce a smear characteristic of a full follicular phase within 14 days, while the latter will produce only slight to moderate changes toward a follicular phase. It seems that 1.25 mg. daily for 7 days, and that amount thereafter every other day for maintenance, will give as complete symptomatic relief for the usual menopausal symptoms as can be obtained with other types of estrogenic therapy.

Complications. Four of the patients studied experienced bleeding during treatment. One bled after taking 1.25 mg. daily for 58 days; two bled after taking 1.25 mg. daily for 7 days and 1.25 mg. every other day for 30 days; one patient had two periods of bleeding after taking a daily dose of 0.31 mg. for 15 days.

The problem of bleeding after estrogen administration causes much concern. This bleeding will occur with the use of any estrogen, if a sufficient amount is given, and is an indication of the potency of the material used. However, the possible presence of unrelated fundal carcinoma makes diagnostic curettage mandatory if bleeding continues longer than a reasonable period following discontinuance of the medication.

Only one patient in the 64 studied complained of nausea after taking this preparation. She had no vomiting. All others were questioned repeatedly and denied gastro-intestinal complaints of any kind. Three patients pointed out particularly, that indigestion was relieved

while taking the natural conjugated estrogen. None of the patients complained of headache, dizziness, tinnitus or other symptom that could be attributed to the therapy.

SUMMARY

A new naturally occurring conjugated estrogen, prepared from the urine of pregnant mares and consisting largely of estrone sulfate, has been used orally in the treatment of 64 women in the menopause. In reasonably small dosage, menopausal symptoms have been well controlled in a majority of the patients. Changes in the vaginal epithelium characteristic of a full follicular phase have followed. The dosage usually has been 1.25 mg. daily for 7 to 14 days, followed by 1.25 mg. every other day for maintenance. Certain advantages appeared in the use of the natural conjugated estrogen over that of diethylstilbestrol. Nausea occurred in only one of 64 cases. A feeling of greater well-being was noted in certain cases who had previously taken diethylstilbestrol. Others noted that symptoms of estrogen insufficiency which usually develop 5 to 7 days following parenteral administration of various estrogens did not occur with continuous oral therapy.

From the observations recorded, it seems that the effect of estrone sulfate is essentially equivalent milligram for milligram, to that of diethylstilbestrol orally on the basis of the effect on the epithelium of the human vagina. The chief objection that can be made to the oral administration of estrogenic products is self-medication. However the steadying, beneficial effect of continuous oral therapy on menopausal symptoms would seem to demand that this method of treatment be used in the future. It is true that this continuous effect may be obtained by the implantation of estrogens, but this is expensive, associated with some discomfort, and is not without some degree of risk.

Therapy of the Menopause

Superiority of Conjugated Estrogens-Equine over Diethylstilbestrol

S. J. Glass, M.D.
and Gordon Rosenblum, M.D.

From the Department of Endocrinology, Cedars of Lebanon Hospital, Los Angeles, California

Since the universal appreciation of the value of estrogens in the endocrine management of the menopause, many commendable efforts have been made to simplify this organotherapy. The search for the most effective estrogens has yielded a number of useful natural and synthetic compounds. The objective sought is one producing maximum symptomatic relief with a minimum of hazard and inconvenience to the patient. These prerequisites are highly desirable because of the chronicity of the menopausal syndrome.

To simplify the therapy of the large number of climacteric patients in this clinic, we have attempted in the past 10 years to limit the estrogens used to the orally effective, naturally occurring compounds, assuming that these are more physiologic for the treatment of the varied menopausal disturbances. We have not tested the newer synthetic steroid hormones nor have we used estrone pellets subcutaneously.

Of the various natural estrogenic compounds previously used, the most satisfactory proved to be a product containing estriol glucuronidate, a natural estrogen.[1] Frequently, in the severe cases it was necessary to resort to preliminary therapy with estrone, or estradiol, parenterally. We could then maintain a physiologic level with 5 to 15 cc. of a solution of estriol glucuronidate daily, although the surgical and radiation castrates occasionally required supplemental series of injections.

With the production of diethylstilbestrol and sodium estrone sulfate[2] we attained our objective in entirely eliminating 'needle therapy.'

Diethylstilbestrol was thoroughly tested in this clinic by Felger and Gendel (1), who reported 78 per cent complete success. In spite of this favorable report we deem the continued use of diethylstilbestrol inadvisable because of *a*) its lack of tonic properties observed in the natural estrogens; *b*) frequency of withdrawal bleeding as a complication; *c*) unknown factors of toxicity as manifested by nausea, skin eruptions and other side reactions. It is our impression that when more sensitive tests for the functions of liver and bone marrow become available, evidence of the toxicity of chronic diethylstilbestrol feeding may yet be demonstrated.

For these reasons we limited the use of diethylstilbestrol to patients with severe menopausal complaints, combining it with estriol glucuronidate. When an effective level was attained, the dosage of diethylstilbestrol was reduced and the drug was finally eliminated leaving the estriol glucuronidate for continued maintenance. This scheme was eminently satisfactory to the majority of patients and obviated the need for hypodermic injections. Although the dosage of diethylstilbestrol was sharply restricted when combined with estriol glucuronidate, nausea and uterine bleeding were occasionally observed.

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[1] Estriol glucuronidate (Emmenin) of Ayerst, McKenna and Harrison, Rouses Point, N. Y.

[2] Sodium estrone sulfate is the substance in terms of which a complex of natural estrogens in pregnant mare's urine is standardized. It is commercially available as Premarin, Ayerst, McKenna & Harrison.

TABLE 1. RESULTS OF THERAPY WITH CONJUGATED ESTROGENS-EQUINE IN 71 MENOPAUSAL CASES

Results[1]	No. Patients	%
Good	58	82
Fair	7	10
Poor	6	8

[1] As in our previous studies, a good result means complete symptomatic relief; fair result means partial relief, while poor result means little or no improvement.

TABLE 2. RESULTS OF THERAPY WITH CONJUGATED ESTROGENS-EQUINE IN 51 CASES OF PHYSIOLOGIC MENOPAUSE

Results[1]	No. Patients	%
Good	44	86
Fair	4	8
Poor	3	6

[1] See footnote to table 1.

When the more potent but untried estrogens from mare's urine became available the use of diethylstilbestrol was first sharply curtailed and finally eliminated from the treatment of the menopausal group.

Preliminary trials[3] in 80 patients gave very satisfactory results when this new preparation was supplemented with minimal doses of diethylstilbestrol. This latter drug was thought necessary for preliminary treatment but it was soon found that adequate dosage of the estrogens-equine alone provided complete symptomatic relief.

This new preparation is available in tablets containing 1.25 mg. of conjugated estrogen expressed in terms of sodium estrone sulfate. When assayed[4] in rats 1.25 mg. yields 600 Collip day oral units of activity. When given to monkeys 1.25 mg. is equivalent, approximately, to 7000 day oral units of estriol glucuronidate. This relatively high effective-ness in monkeys probably holds true for women and explains the efficiency of moderate dosages of sodium estrone sulfate in controlling menopausal symptoms.

TABLE 3. RESULTS OF THERAPY WITH CONJUGATED ESTROGENS-EQUINE IN A GROUP OF 20 PATIENTS WITH ARTIFICIAL MENOPAUSE

Results[1]	No. Patients	%
Good	14	70
Fair	3	15
Poor	3	15

[1] (See footnote to table 1).

TABLE 4. FREQUENCY AND TYPE OF REACTIONS TO CONJUGATED ESTROGENS-EQUINE IN THERAPY OF THE MENOPAUSE

a) Abnormal bleeding Questionable—this patient has intrauterine pathology which is being investigated	1 case
b) Nausea Questionable—this patient has proven gallbladder disease	1 case
c) Skin eruptions	0
d) Headache	0
e) Intolerance for any reason	0
f) Patients noting resumption of menses	7

TABLE 5. COMPARISON OF CASE SERIES STUDIES FROM THE ENDOCRINE CLINIC

	Number of Cases	Results			Reactions		
		Good	Fair	Poor	Nausea	Bleeding	Miscellaneous
Diethylstilbestrol alone (Felger & Gendel)	74	78%	8%	14%	37%	frequent	15%
Estrogens-equine and diethylstilbestrol	80	86%	9%	5%	1%	8%	0
Conjugated estrogens-equine	71	82%	10%	8%	1[1]	1%[1]	0

[1] Questionable (see table 4)

The present report is based on the treatment of 71 menopausal patients for 6 to 10 months with sodium estrone sulfate. Initial dosages varied from 2.5 to 3.75 mg. daily. This was

[3] Read at the annual session of California Medical Association, May 6, 1942.

[4] Personal communications by Drs. J. Murray Scott and J. B. Collip.

gradually reduced to 1.25 mg. daily. Maintenance was possible eventually with 1.25 mg. 3 to 5 times weekly.

Tables 1 to 5 summarize the experience of the past 4 years with oral estrogens in the menopause. It is evident that sodium estrone sulfate is more effective in the majority of cases and does not produce the side reactions observed with the stilbestrol series. The absence of bleeding with the use of the conjugated estrogens-equine is a distinct advantage.

DISCUSSION

These favorable results have justified discontinuing the use of diethylstilbestrol in routine therapy in the menopause and the substitution of sodium estrone sulfate for all other estrogens. The problem of the routine care of our climacteric patients has been simplified. The group of 34 patients previously treated with diethylstilbestrol reported not only relief from flushes but a striking improvement in the sense of wellbeing. As noted in table 4, reactions are rarely seen. Cyclically recurring bleeding was restored to 7 patients who complained of preclimacteric symptoms such as irregular menses or brief periods of amenorrhea. This bleeding in every way resembled normal menses.

Failures of therapy with sodium estrone sulfate are few indeed and chiefly confined to those patients with strong psychoneurotic tendencies. This limitation is true, however, for all estrogens; the problem is not one for organotherapy alone, supplemental psychotherapy being used.

The results of this limited experience with the new estrogens-equine are more gratifying than any obtained with other oral estrogens. The gradual replacement therapy which is possible with moderate dosage is particularly desirable. From its use one may anticipate a smoother readjustment of the internal environment of the climacteric female. The potent pharmacodynamic properties of the synthetic estrogens, in the dosage commonly prescribed, probably interfere with the normal transitional changes incident to the climacteric.

SUMMARY

A preparation containing a complex of natural estrogens from the urine of pregnant mares has been found, in our clinic, to be a safe, effective, orally active therapy for the relief of the climacterium. It gives to the patient a feeling of well being which is not produced by the synthetic compounds.

We are grateful to Dr. J. Murray Scott of Ayerst, McKenna & Harrison for the supply of Premarin, used in this study.

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Oral Use of Conjugated Estrogens-Equine

ELMER L. SEVRINGHAUS, M.D.
AND RUTH ST. JOHN, M.D.

From the Department of Medicine, University of Wisconsin, Wisconsin General Hospital, Madison, Wisconsin

ESTROGENIC substances are recognized to be active when taken orally, although the physiologic effects obtained from a given dose of the several natural estrogens vary widely in intensity. Clinical success has been secured in relief of climacteric symptoms by use of the three purified estrogens, estradiol, estrone, and estriol, and also by two relatively impure preparations, 'estrogenic substance' and estriol glycuronide. The latter material represents an exception to the usual practice of chemical treatment of the source materials in order to obtain the estrogenic molecules free from the glycuronic or inorganic acid combination in which estrogens are excreted in the urine. The free estrogens are very poorly soluble in water. Estriol glycuronide[1] is a water-soluble form of excreted estrogen and has been found useful in relief of patients who did not require large amounts of the hormone. An attempt to secure a more potent estrogen which is similarly water soluble and conjugated has led to the production of a new type of orally active hormone. This is estrogens-equine. It has been found unnecessary to reduce this compound to a state of crystalline purity, so far as clinical use is concerned. The standardization of such a material depends, however, on comparison with permanent reference standards of purified sodium estrone sulfate. This comparison may be made biologically or chemically, employing the color reactions (1) which are characteristic of the natural estrogenic molecules. There are distinct advantages to the chemical methods. The preparations of this new orally active estrogen are being distributed in tablets which contain 1.25 mg. of the conjugated estrogens.[2]

Continuing an experience one 15 years by one of us in the comparisons of various estrogenic substances for treatment of women with the menopause syndrome (2), it has seemed worth while to observe the effectiveness of this new preparation for this same purpose. The earlier trials were made with capsules of crude concentrated substance, but all the patients reported herein have used the tablets currently available commercially. The only observable difference has been that a few women noted a slight nausea after using the capsules, but this was not constant. No such reaction has been reported by those using the sugar-coated tablets now provided. It is gratifying to be able to assert that in the entire series of 25 women reported there have been no unpleasant side effects from using the estrogens-equine as now available. This is contrasted with the intolerance noted by a few patients to the synthetic estrogen, diethylstilbestrol and its derivatives (3). The freedom from unpleasant effects with conjugated estrogens-equine is directly comparable to our extended experience with the other natural estrogens.

The most obvious question to be determined is the genuine estrogenic potency of the ma-

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[1] The only preparation of estriol glycuronide used clinically is Emmenin, produced by Ayerst, McKenna and Harrison, Ltd., Rouses Point, N. Y. and Montreal, Que.

[2] The name "Premarin" has been assigned to the substance, which is derived from (pre)gnant (mar)e's ur(in)e by processes developed in the laboratories of Ayerst, McKenna and Harrison. It is actually a mixture of conjugated estrogens. Premarin has been supplied through the courtesy of Dr. A. Stanley Cook, Director of the Research and Biological Laboratories, Ayerst, McKenna and Harrison, Ltd., Montreal.

terial in question. This has been demonstrated by study of the vaginal epithelium obtained by pipette samples and stained by the technique of Shorr (4). Prompt and marked increases in estrogenic activity have been demonstrated with dependable regularity when women received from 1.25 to 5 mg. (1 to 4 tablets) daily. In figure 1 are shown the vaginal smears before and after two weeks of therapy with 1.25 mg. twice daily. This transformation has been demonstrated in 9 of the women who had undergone bilateral oöphorectomy as well as in an equal number of those with a spontaneous menopause, leaving no doubt as to the activity of the preparation in the form administered.

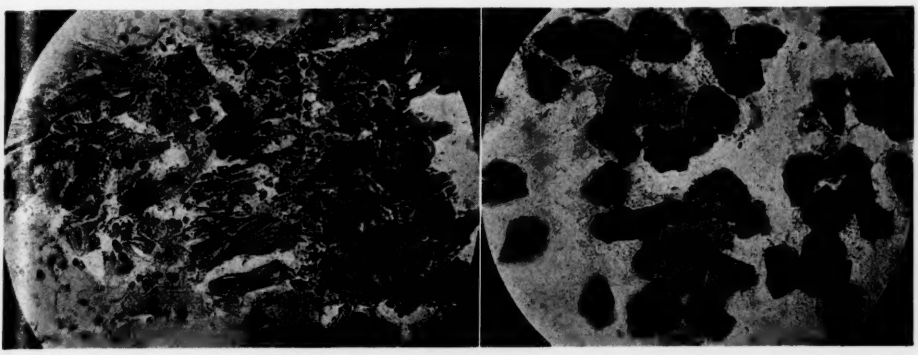

FIG. 1. VAGINAL SMEAR SHOWING ESTROGENIC ACTIVITY before and after the use of conjugated estrogens-equine. *Left*, atrophic smear. *Right*, 4 plus activity.

Further evidence of this potency is supplied by the occurrence in two of our patients of vaginal bleeding following treatment with the estrogens-equine. There had been no such flow for 19 years previously in one 61-year-old woman. In the case of the other woman with bleeding there had been an oöphorectomy and subtotal hysterectomy 9 years before. Similar experience is well known following use of natural or synthetic estrogens. We believe that optimal doses of any estrogen are those which are below the level which will cause such bleeding. This level is not difficult to maintain with conjugated estrogens-equine, but the possibility of producing such disturbance must be kept in mind as a limiting factor in dosage.

The degree of satisfaction expressed by our patients has been most gratifying. Of 25 women who have used this new preparation long enough to make comparisons with other estrogens all save 3 were entirely satisfied. Among these 3 was one who has a longstanding vasomotor instability, not relieved by any estrogen, natural or synthetic, even though other climacteric symptoms were held in abeyance. Her disappointment with this estrogen is not a real objection. Of the other two, who preferred to use diethylstilbestrol, one was a young woman with high grade allergic gastro-intestinal disturbance which produced a syndrome resembling anorexia nervosa, including a long period of secondary amenorrhea; the other was a very nervous woman with an artificial menopause who tolerated and benefited from the use of large doses of stilbestrol derivatives. Nevertheless it was shown in both of these women that conjugated estrogens-equine caused a striking formation of cornified epithelium in the vaginal smears.

Of the 22 women completely relieved of climacteric symptoms there were 11 with spontaneous occurrence of the menopause and 11 in whom surgical removal of ovaries was known to have preceded the symptoms. The ages of the 25 women ranged from 31 to 62 years, with 5 women in the fourth decade, 11 in the fifth, 8 in the sixth, and only 1 in the early seventh decade of life.

Comparison of the results with use of the other estrogens in the same women is of importance in an attempt to determine the relative value per dollar of cost to the patient (3). The results in 19 such parallel instances are presented in table 1. These are not to be taken as definite equations, for there was not gradual

enough change in dosage of either conjugated estrogens-equine or the other estrogens to make sure of exact equivalence. The comparisons are made on the basis of substantially similar vaginal smear responses to the drugs and doses listed, when there was no clinical reason to believe a significant alteration had occurred in the status of the climacteric picture. In other words, the equations are based on direct transfers from one drug to the other, with periods of several weeks of treatment allowed for each drug before results were evaluated. It will be seen that in the observations made by changing from either one of three brands of estrogenic substance, used orally, to the estrogens-equine, the conclusion is justified that a tablet containing 1.25 mg. of the latter is always *a*) at least as potent as 2000 international units of estrogenic substance, *b*) is commonly found better than this, and *c*) may be better than 5000 units. A similar judgment is recorded about diethylstilbestrol, suggesting that 1.25 mg. of the conjugated estrogens is at least as effective as 0.1 mg. of the synthetic compounds and probably comparable to 0.3 to 0.5 mg. The competitive place of conjugated estrogens-equine will consequently vary with the changes in price of these several estrogens. It may be stated with assurance that, based on retail prices of natural estrogens current in the latter half of 1941, this new preparation was at least as effective per dollar as the other natural estrogens. Maintenance doses have never been higher than 1.25 mg. 3 times daily. An occasional patient has been kept entirely comfortable with 1.25 mg. on alternate days.

TABLE 1. COMPARISON OF RELATIVE POTENCIES OF CONJUGATED ESTROGENS-EQUINE AND OTHER ESTROGENS

Estrogen Previously Used	Conjugated estrogens-equine (standardized on basis of sodium estrone sulfate) 1.25 mg.			
	Seemed as potent as	No. of trials	Seemed more potent than	No. of trials
Estrogenic substance (3 brands)	2000 I.U. 4000 I.U.	1 1	2000 I.U. 3000 I.U. 4000 I.U. 5000 I.U.	4 1 1 1
Estrone, alcohol solution applied on the skin	300 I.U.	1		
Estradiol	0.50 mg.	2		
Diethylstilbestrol	0.1 mg. 0.3 mg. 0.5 mg.	2 1 2	0.2 mg. 0.3 mg.	1 1

SUMMARY

Clinical experience with oral administration of tablets of conjugated estrogens-equine, in doses of 1.25 mg., one to three times daily, has shown this new variety of estrogenic preparation from pregnant mare's urine to be a dependably helpful agent in giving complete relief from the common autonomic, emotional and mental complaints of the menopausal syndrome.

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The Significance of Ketosis

[A Review Article]

EATON M. MACKAY

From The Scripps Metabolic Clinic, La Jolla, California

BY KETOSIS we understand the occurrence or accumulation in the blood in significant amounts of the so-called ketone bodies, namely beta-hydroxybutyric acid, acetoacetic (or diacetic) acid and, secondarily, acetone. In normal subjects on a general diet ketone bodies are present in the blood in inconsiderable amounts (Barnes and Wick, 1939). They appear in largest quantities in cases of severe diabetes and with normal subjects only when fasting or when the food carbohydrate is greatly restricted. Hirschfeld in 1895 (42) first showed that the factor common to these conditions and responsible for the ketosis is the absence of carbohydrate from the food or, as in the diabetic, from his metabolism. Today there is no question that ketosis is due to carbohydrate lack.

Antiketogenesis versus Ketolysis

Our ideas of how carbohydrate lack produces a ketosis have undergone many alterations. The old idea, first advanced by Geelmuyden in 1909 (39), that the ketone bodies represented incomplete oxidation products of the fatty acids which required the concomitant oxidation of carbohydrate metabolites for their utilization gained many adherents (93, 100, 94, 51) and the so-called 'ketogenic-antiketogenic' ratio (Shaffer, 1923) which implied a quantitative relationship between the oxidation of ketone bodies and glucose became widely accepted. The view expressed in the oft quoted dictum of Rosenfeld, 1906, that 'Fats burn only in the fire of carbohydrates' and the later remark of Woodyatt (1910) that 'when the mixture of metabolites oxidizing in the body contains more than three molecules of higher fatty acids to one of glucose, then the body "smokes" with acidosis compounds like an automobile smokes with too much oil in the cylinders,' have governed the conception of ketosis until very recently. It is now believed that the oxidation of the ketone bodies is not influenced by the presence or oxidation of glucose and few workers in the metabolic field still hold the idea that glucose exerts a ketolytic action. The ketogenic-antiketogenic ratio is largely of historical interest.

Although it is now generally accepted that the influence of glucose and glucose-formers on ketosis is in the nature of an antiketogenic action and not one of ketolysis, Deuel and his co-workers adhere to the ketolytic theory (1938, 1940). They advance the evidence of Shapiro, 1935, that the feeding of any glucose precursor diminishes the ketonuria when acetoacetate is fed to fasting rats. In such rats the ketosis is the sum of the acetoacetate fed plus the normal fasting ketosis and the influence on the latter of any alkali freed by catabolism of the acetoacetic acid with which it is fed (MacKay et al. 1941a). Glucose or any precursor simply reduces or abolishes the fasting ketosis through its effect upon ketone body production by the liver. The blood ketone level is then not sufficiently high to support as large or even a measurable ketonuria. Deuel et al. (1938) conclude that since the metabolism of alcohol may spare fat, and alcohol is not antiketogenic, glucose cannot exert its effect through antiketogenesis. This reasoning involves the unwarranted assumption that all fat-sparing agents and alcohol and glucose in particular fill the same metabolic requirements. The reduced ketonuria produced by glucose in fasting rats following a low-protein diet or receiving sodium butyrate (Deuel, et al. 1938) only means that the ketosis has been reduced by the sugar. The authors emphasize the small percentage of the total metabolism represented by the dose of sugar which is antiketogenic. That such small quantities of glucose have a measurable influence upon a fasting ketosis is evidence for the glucose lack which causes the condition.

Deuel et al. (1940) found that the apparent rate of utilization of sodium beta-hydroxybutyrate injected into nephrectomized rats was less in those which had been fasting than in those which had been fed glucose. Used by these investigators as evidence for ketolysis by glucose, this difference may be explained much more reasonably. They gave the acid mostly in the

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form of its sodium salt (pH 7.4) and in very large doses. As the beta-hydroxybutyric acid was catabolized alkali was freed which would be ketogenic (MacKay et al. 1941a) in the fasted rats but could not contribute to the ketosis in the glucose-fed rats. This endogenous ketone production due to alkalosis was not corrected. In a similar experiment using doses of only one-third as much beta-hydroxybutyrate Mirsky et al. (1939) found no difference between the rate of utilization by fasted and fed rats.

Bobbitt and Deuel (1942) have recently presented data on liver slice metabolism which they interpret as favoring ketolysis. Having the living tissue in such unnatural conditions makes it extremely hazardous to draw conclusions applicable to the intact animal from data of this nature. But quite apart from this the large variability in their results and the very small difference in the rate of butyrate and ketone body disappearance in the liver-slice substrate with glycogen as compared with the substrate without glycogen make it difficult to evaluate the significance of their data.

Opposed to the meager data which may be interpreted as supporting ketolysis is the large bulk of almost irrefutable evidence for antiketogenesis as being the action of carbohydrate in ketosis.

Origin of Ketone Bodies

It was early recognized that the ketone bodies must originate from the fatty acids of fat and possibly to a small extent from a part of some of the amino acids in protein (Magnus-Levy, 1908, Lusk, 1928). There is no evidence that glucose or any carbohydrate metabolite such as lactic or pyruvic acid yields ketone bodies except as they may form fat or glucose and then fat, a process in which glucose fails to take part during ketosis. Acetoacetic acid is generally the initial ketone body and may undergo reduction in various tissues to beta-hydroxybutyric acid (Wakeman and Dakin, 1910–11; Marriot, 1914) or break down in small amounts to form acetone. The production of acetoacetic acid by the oxidation of fatty acids is intimately associated with the beta-oxidation theory of Knoop (1904). We now know that this theory cannot account for the large amount of ketone bodies which fatty acids are known to yield. A modification of Knoop's theory (Toenniessen and Brinkmann, 1938; MacKay et al. 1940a and c; Wick, 1941) accounts for the amount of ketone bodies formed by fatty acids and explains the discrepancies between various experimental data and the older theory.

It had long been accepted (Dakin, 1909; Jowett and Quastel, 1935) that the ketone bodies arise by successive beta-oxidation of natural fatty acids. This would give only one molecule of ketone body (beta-hydroxybutyric or acetoacetic acids) per molecule of the higher fatty acids (C_{14}, C_{16}, C_{18}). During recent years evidence has been obtained by numerous investigators that much more than one molecule of ketone body acid is obtained from one molecule of a higher fatty acid. In a study of the oxidation of fatty acids by isolated liver slices Jowett and Quastel (45) found a larger quantity of ketone bodies than successive beta-oxidation, as usually conceived, would account for. This observation has been confirmed by Stadie et al. 1941. Deuel and his co-workers in 1935 and 1938 (17, 25) observed a far greater yield of ketone bodies from the higher fatty acids in feeding experiments in rats than Knoop's hypothesis would provide for. Blixenkrone-Moeller in 1938 compared the oxygen consumption of perfused livers of diabetic cats with the total ketone body production and could explain the low oxygen-ketone body ratio only by assuming that four molecules of ketone body were formed per molecule of fatty acid. This observation has been confirmed in isolated liver slices by Stadie et al. 1940. These observations have made Knoop's successive beta-oxidation theory in its original form untenable.

Two new theories for the mechanism of ketone body production have been proposed. Both of them assume that all of the fatty acid molecule may be converted to ketone bodies. One of these is the 'multiple alternate oxidation' theory first proposed by Hurtley (1915–16) and elaborated by Jowett and Quastel (1935). This assumes that a fatty acid is oxidized at alternate carbon atoms simultaneously along the whole length of the chain. The C_4, C_8, C_{12}, C_{16}, and C_{20} acids would be entirely converted to ketone bodies while the intermediate acids would have two carbon atoms from each molecule completely oxidized at once or forming some other compound.

The other new theory of ketone body formation (MacKay et al. 1940a) is based upon classical beta-oxidation. As proposed, it assumes, as has generally been taken for granted, that the two carbon atoms dropped from the chain by successive beta-oxidation form acetic acid. But it should be emphasized that although acetic acid appears to be a likely intermediary it is possible that some other two-carbon compound is formed instead. Whether it be acetic acid or some other compound it is assumed that this condenses to acetoacetic acid. A molecule of C_{18} acid and two molecules of C_{14} acid would give 4 and 7 molecules of ketone body, respectively. In the light of our present knowledge this 'beta-oxidation-condensation hypothesis' seems to be the most applicable to the various observations which require explaining.

All of the data which have been advanced as evidence (45, 17, 25, 86, 87, 11) in favor of 'multiple alternate oxidation' serves equally well in support of our theory. Besides this the beta-oxidation-condensation scheme will apply to many observations which it is impossible to explain by multiple alternate oxidation. Deuel et al. (1936) met difficulties in applying the latter when

more ketone bodies were obtained from caproic (C_6) than butyric (C_4) acid. Valeric acid (C_5), three carbon atoms of which forms glycogen, is known (Leloir et al. 1939; MacKay et al. 1940c) to form ketone bodies. The beta-oxidation-condensation theory easily explains both of these observations as well as the behavior of branched chain fatty acids in relation to ketone body formation (Wick, 1941). None of these facts can be reconciled with multiple alternate oxidation.

The experiments reported by Morehouse and Deuel (1940) on ketone body formation from deuterium containing caproic acids are excellent support for the beta-oxidation-condensation theory. An average of 6.4 per cent of the beta-hydroxybutyric acid excreted contained deuterium after feeding alpha-beta-deutero-caproate. If the beta-hydroxybutyrate had originated solely by beta-oxidation no deuterium would have been present in it because the deuterium on the beta carbon atom would be replaced by a carboxyl group. But condensation of the two carbon intermediary removed by beta-oxidation would retain deuterium in the ketone bodies.

Although it is not essential to the beta-oxidation-condensation theory that acetic acid be the intermediary product it appears to be a likely possibility (MacKay at al. 1940a). Toenniessen and Brinkmann (1938) believe it is. There is plenty of evidence for increased ketone body formation in the liver (Loeb, 1912; Friedman, 1913; Leloir and Munoz, 1939; Jowett and Quastel, 1935) and in intact animals (MacKay et al. 1940a) by acetic acid. By the use of the heavy isotope of carbon Swendseid et al. (1942) have shown that acetic acid actually takes part in the synthesis of the ketone bodies. Hurtley (1915–16) originally proposed his theory because he failed to find butyric and acetic acids in ketone producing livers. Acetic acid was not found in ketonic liver slices by Stadie et al. (1941). These investigators were apparently unaware of the difficulty of recovering acetic acid which is closely bound by plasma and tissue proteins (Lehninger, 1942). Wakeman and Dakin (1909) appear to have been well aware of this difficulty and employed heroic means in an attempt to determine whether or not acetic acid was produced in the liver. It is interesting that Lehninger (1942) has found a catalytic system in rabbit-muscle mince which forms acetic acid from acetoacetic acid.

There are at least two types of fat oxidation which may take place in the mammalian organism. In one type, which occurs under certain conditions of carbohydrate lack, ketone bodies are produced. This kind of fat oxidation is localized in the liver for there is now agreement that this organ is the only significant source of the ketone bodies which appear in the blood in ketosis (Edson, 1936; Burn and Marks, 1926; Raper and Smith, 1926–27; Chaikoff, 1927; Embden and Kalberlah, 1906; Mirsky, 1936a, b; Blixenkrone-Moeller, 1938; Harrison and Long, 1940; Crandall et al., 1940–41). In the other type of fat oxidation the liver is not directly involved for there is good evidence of the utilization of fat in fasting animals after hepatectomy (Markowitz, 1927–28; Drury and MacMaster, 1929). If ketone bodies are formed during the course of fat oxidation in muscle or other extra-hepatic tissues they are further oxidized within the cells of these tissues for such fat oxidation supplies no ketone bodies to the blood in ketosis.

Utilization of Ketone Bodies

Although it has long been known that the body tissues are capable of utilizing ketone bodies (Marriot, 1914; Snapper and Greenbaum, 1938; Chaikoff and Soskin, 1928; Friedmann, 1936), the importance of this utilization was only recognized in recent years by Drury (4, 7) and independently by Blixenkrone-Moeller (10, 12). This realization of the extent of ketone body utilization has completely altered our conception of the significance of ketosis. The ketone bodies may no longer be looked upon as noxious substances which are necessarily deleterious to the organism. It has been shown that the ketone bodies are utilized equally as well by the peripheral tissues in conditions of diabetic and fasting ketosis (Chaikoff and Soskin, 1928; Barnes and Drury, 1937; Barnes et al. 1940) as when there is no ketosis. Acetoacetic and beta-hydroxybutyric acids appear to be utilized to the same degree. One of the most important factors governing the utilization rate of the ketone bodies is their concentration in the blood (Barnes et al. 1938; Wick and Drury, 1941; Nelson et al. 1941). They are used preferentially in the presence of useable glucose (MacKay and Barnes, 1936) so carbohydrate is without influence upon the utilization rate in either the heart-lung preparation (Barnes and Drury, 1937; Waters et al. 1938) or the intact organism (Mirsky and Broh-Kahn, 1937; Mirsky et al. 1939; Dye and Chidsey, 1939). Under certain experimental conditions as much as 90 per cent of the calories consumed by the organism may be accounted for by ketone bodies (Wick and Drury, 1941). From 30 to 80 per cent of the energy requirements of the tissues in ketogenic states may be supplied by the combustion of

the ketone bodies (Barnes et al. 1940; Crandall et al. 1940–41). The level of the ketone bodies in the blood is, of course, determined by the difference between their rate of production by the liver (22) and their use by the other tissues (7). Besides the concentration in the blood, the other important factor regulating the rate of utilization of the ketone bodies by the peripheral tissues is the metabolic rate (Mirsky and Broh-Kahn, 1937; Drury and Wick, 1941). When the metabolic rate is increased by exercise (Blixenkrone-Moeller, 1938; Drury, Wick and MacKay, 1941) or greater thyroid activity (Mirsky and Broh-Kahn, 1937) there is an increased utilization of these substances. It is probable that increases in the metabolic rate during ketosis result in an increase in the rate of production of the ketone bodies as well (Drury, Wick and MacKay, 1941).

Regulation of Ketone Body Production

There are various views as to how carbohydrate lack regulates the onset and extent of ketone body formation by the liver. An inverse relation between the glycogen content of the liver and ketone body formation was first emphasized by Embden and Wirth in 1910. This is not surprising for carbohydrate lack would tend to be associated with low, and carbohydrate feeding with higher, liver glycogen values. Many investigators have been of the opinion that there is a critical glycogen concentration in the liver below which ketosis ensues (Mirsky, Nelson and Grayman, 1939). Recent reviewers (Soskin and Levine, 1941) believe that the glycogen level itself may be the critical factor or it may be merely a reflection of increased glycogenolysis. Mirsky (1936b) once favored the rate of glycogenolysis as being all important and this view is embraced by Somogyi in 1940 (82, 83). Mirsky has now returned (1942) to the idea (70) that the glycogen concentration is the regulatory factor. It has been suggested by Mirsky, 1942, and Soskin and Levine, 1941, that the mechanism whereby glycogen functions to govern ketone body production is by competition for the enzyme system concerned with the conversion of fatty acids to ketone bodies (Embden and Kalberlah, 1906). It is very difficult to correlate this or any similar idea with the fact that short chain even-numbered carbon (MacKay, Wick and Barnum, 1940b) as well as odd-numbered-carbon fatty acids (MacKay, Wick and Barnum, 1940c), which are stored by the organism with difficulty or not at all, form ketone bodies even when the liver is loaded with readily available glycogen. It is true that much of the evidence may be fitted in (Soskin and Levine, 1941; Mirsky, 1942) with the scheme that the liver glycogen level regulates ketone body production, but there are many other discrepancies which are difficult to explain. For instance in extended fasting the ketosis has not reached its maximum when the liver glycogen is at its lowest concentration and the ketosis continues and becomes stabilized although the liver glycogen increases to a significant concentration (Wick and MacKay, 1940). Under most circumstances the level of the liver glycogen and even more so the rate of hepatic glycogenolysis is apt to reflect the glucose demand of the organism and it is probably because of this that they have appeared to be the determining factors in the onset of ketosis.

The most reasonable theory[1] for explaining the significance of ketosis and the regulation of ketone body production in the liver would seem to be as follows. All of the evidence indicates that we must look upon ketosis as a normal mechanism for the utilization of fatty acids. It consists of a partial oxidation of these substances to form ketone bodies by the liver and distribution of these ketone bodies to the tissues by the blood for complete combustion. Our present knowledge indicates that the intermediary transformation of fatty acids to ketone bodies is a supplementary mechanism operating when there is a shortage of carbohydrate for fuel. This shortage may be absolute, due to the almost complete absence of glucose from any source, or relative, due to an inability of the tissues to utilize glucose which is present. Apparently there are at least two forms in which fuel is supplied to the tissues. One of these is fat which is used directly by the tissues. The other form of fuel is usually supplie by glucose and in ketosis by glucose and the ketone bodies. We will call this 'quick fuel' on the assumption that glucose and the ketone bodies are easily oxidized in comparison with far. This is true *in vitro* and whether or not this situation exists *in vivo* is of no consequence here. It is sufficient that these compounds be-

[1] This theory was first proposed in its major aspects some years ago (Metabolic Discussion Group, Federation of American Societies for Experimental Biology, 1937) as a result of Drury's realization (4, 7) of the importance of ketone body utilization. The idea has been briefly alluded to from time to time (MacKay and Barnes, 1938)—"It is possible that with this dearth of readily oxidizable carbohydrate upon which the organism is so dependent it turns to the ketone bodies when they are available for quick energy yielding substances. It is interesting in this connection that ketone bodies are always produced under those circumstances when there is an absolute lack of glucose or a relative deficiency of oxidizable glucose available for the body economy. It is hoped that a new . . . method . . . may make it possible to determine the purposefulness of a ketosis in supplying oxidizable fuel of the order of glucose when the latter is unavailable." Crandall et al. (1940–41) have lately considered this idea at some length and consider ketosis as a phase of 'glucoprivia' metabolism. Recent reviewers (Soskin and Levine, 1941; Mirsky, 1942) have accepted the theory only in part.

have differently from ordinary fatty acids. It is necessary to recognize two types of 'quick fuel' requirements by tissues *a*) one peculiar to the brain and peripheral nervous tissues and *b*) a second shared by all other tissues. The quick fuel requirement of the former is high and practically constant under all conditions (Mulder and Crandall, 1941). Here all of the quick fuel requirement must be supplied by glucose. The quick fuel requirement and the glucose utilization rate are in this case identical.

The quick fuel requirement by the tissues other than those of the nervous system varies greatly according to circumstances. Under ordinary conditions it is covered entirely by glucose and the glucose utilization rate is then the same as the quick fuel requirement. However, this is not always the case and although none of this quick fuel requirement may be replaced even in part by fatty acids, it may be replaced in part or entirely by ketone bodies. The ketosis mechanism probably exists because of the inability of the mammalian organism to convert fat to glucose. There is good evidence for the purposefulness of ketosis in the usefulness of the ketone bodies to the tissues under the conditions in which they occur when there is always a reduction in the amount of glucose available.

The theory of ketosis outlined here necessitates the regulation of ketone body production in the liver by the demand for glucose by the neural tissues and for glucose or a substitute by the extra-neural tissues. It may well be that the demand for the production of ketone bodies is a device designed to conserve glucose for the central nervous system.

At present we are able to measure this demand for quick fuel only as the rate of utilization of glucose. This includes glucose which is stored as glycogen and fat as well as that which is oxidized. There is a possibility that only the portion of the glucose utilization which is oxidized is concerned with governing ketone body production. We can only speculate about this point. It is presumed that the actual onset and regulation of ketone body production is under the control of some brain center such as the hypothalamus in which are centered so many of the homeostatic mechanisms of metabolism. Action upon the liver could come about via neural or humoral routes. The close connections between the hypothalamus and the pituitary and the well-known influence of the anterior pituitary on ketosis (Anselmino and Hoffman, 1931; Burn and Ling, 1933; Houssay, 1936) is suggestive of the latter.

Mention should be made of an odd type of ketosis which at first glance appears to be an exception to the general rule. Ketone bodies are formed when short-chain odd or even-numbered carbon fatty acids are fed under conditions (MacKay et al. 1940 b and c) in which the glucose supply is adequate and there is no reason to suppose that there is a reduction in glucose utilization. Fatty acids of this kind are not found in body fat and occur in the food in very small amounts or not at all. Apparent inability of the organism to store these fatty acids probably leads to their rapid disposal and ketone body formation could aid this. Barnes (8) has made a novel suggestion as to how this may come about. He reasons that the formation of ketone bodies by short chain fatty acids in well-fed animals having an adequate glucose supply is as follows: In the fed organism without ketosis fatty acids are being burned by the tissues of the body through beta-oxidation. The two-carbon compound thus formed (possibly glyoxylic acid which unlike acetic acid may form ketone bodies in the fed organism) is immediately burned by the cell or tissue where formed and never reaches the liver. On fasting, or under those conditions similar to fasting in that there is ketosis, the two-carbon compound is not burned as easily by the tissues. Being a small molecule it gets into the blood stream and goes to the liver to form ketone bodies. Any fat oxidation which took place in the liver would always form ketone bodies; the liver being free from the influence of fasting as it affects the extra-hepatic tissues. The latter then use the ketone bodies with ease. The short-chain fatty acids which give rise to ketone bodies in the normal fed organism are either stored by the body tissues with difficulty or not at all. Consequently they are oxidized in the liver, a process of fat utilization which presumably gives ketone bodies under any conditions according to Barnes' idea.

Fasting Ketosis

The ketosis of fasting is due to an almost complete lack of carbohydrate. When there is no food supply the liver sets free glycogen and starts converting protein to glucose. After the third or fourth day of fasting the glucose needs of the body are supplied by the liver almost entirely from conversion of protein from the general body tissues. During extended fasting only a small fraction of the total fuel requirement of the tissues is supplied by glucose, perhaps not more than 10 per cent (Drury, 1942). In view of the fact the fuel required by the central nervous system seems to be almost en-

tirely glucose it is possible that the requirement of this tissue accounts for all of the glucose produced and oxidized in the fasting organism. Support for this view is furnished by the nature of the relation of the utilization rate of the ketone bodies (beta-hydroxybutyric acid) to their concentration in the blood. The utilization is dependent on the latter but the upper limit of utilization seems to be reached when the oxidation of this substance uses about 90 per cent of the oxygen consumed by the organism (Wick and Drury, 1941). A normal individual will derive about 90 per cent of his energy from the combustion of fat after a 48-hour fast. Under such conditions he would show a moderate ketonemia (Wick, et al. 1940; Drury and Wick, 1941; Drury, Wick and MacKay, 1941) of 20 to 40 mg. per cent. At such concentrations only about half of the total metabolism of the tissues would be taken care of by ketone body oxidation; the remainder of the fat oxidized would presumably be burned directly in the tissues.

It may be presumed that the ketosis of fasting develops because the glucose requirement of the tissues cannot be met by the meager source of sugar available to the organism. Since protein catabolism is the only source of glucose (except for a fairly constant amount of glycerol from fat) after the initial stages of fasting it is not surprising that there is an inverse relation between the protein breakdown as measured by the excretion of nitrogen in the urine and the level of ketone bodies in the blood (MacKay et al., 1941b). Fasting appears to reduce the portion of the quick fuel requirement which could be covered with glucose were it available, for Bergman and Drury (1937–38) have shown that a pre-operative fast of 4 days diminishes the sugar requirement (utilization) of the eviscerated rabbit by 50 per cent. This may aid in the preferential use of the ketone bodies which become available.

Increased metabolism due to exercise increases the quick fuel requirement and during fasting when glucose is not available this is met by an increased utilization (Drury and Wick, 1941; Drury, Wick and MacKay, 1941) and production (31) of ketone bodies. When the metabolic rate is increased by an artificial fever something of the same kind occurs.

There is a marked sex difference in ketosis (Deuel and Gulick, 1932), the female developing a greater fasting ketosis than the male. A comparison of the nitrogen excretion of the two sexes during fasting (Grunewald, Cutler and Deuel, 1934) suggests that either protein is better conserved by the female or the amount of stored protein available to form glucose is greater in the male. Pregnancy increases fasting ketosis (Burn and Ling, 1933; MacKay and Barnes, 1936). Data are not available but there is every reason to suppose that the quick fuel requirement is increased in this condition.

Fasting ketosis is reduced by a mineral acid acidosis (MacKay et al., 1941a) and by dehydration (MacKay and Visscher, 1941c). Protein catabolism is increased in this condition and supplies additional glucose to meet the demand for quick fuel. An alkalosis (58) reduces protein catabolism during fasting and increases the degree of fasting ketosis.

Besides in fasting, ketosis occurs in the normal organism as a result of the so-called ketogenic diet. This simply means a food mixture, high in fat and low in carbohydrate (both preformed and as protein) which resembles the metabolic mixture which the organism obtains from its own tissues during fasting. The quick fuel requirement is too large to be met by the glucose supplied in the diet and ketosis ensues.

Just as glucose production, storage and utilization are profoundly affected by the glands of internal secretion so do the secretions of these organs participate in the occurrence and control of ketosis. This action is in part by way of the regulation of glucose metabolism and possibly partly direct. The picture is still obscure and much remains to be learned. An increase in the metabolic rate produced by experimental hyperthyroidism (Mirsky and Broh-Kahn, 1936; 1937) increases the glucose utilization rate. Consequently injected beta-hydroxybutyric acid is used at an increased rate under these conditions. Epinephrine liberates stored sugar into the blood and in fasting temporarily depletes the supply of available glucose. There is a rise in heat production and oxygen consumption and almost certainly in the demand for quick fuel. An enhancement of ketone body production results (Anderson and Anderson, 1927). The anterior pituitary is all important

in the occurrence of ketosis and the regulation of ketone body production. Extracts of the anterior pituitary have been prepared (Anselmino and Hoffman, 1931; Burn and Ling, 1933) which produce a great increase in a fasting ketosis. It is uncertain as to whether this influence is indirect through an effect upon the quick fuel demand and the portion of it supplied by glucose or a direct effect upon the ketone body type of fat metabolism. The latter seems to be most likely for in the hypophysectomized mammal ketosis does not occur (Houssay, 1936) even when the amount of glucose available is obviously far less than the quick fuel demand. The part played by the hormones of the adrenal cortex in the regulation of ketosis must await further study before it may be expressed with any degree of certainty.

Ketosis in Diabetes Mellitus

A disposition to develop ketosis is one of the main characteristics of the diabetic. In fasting the demand for glucose by the tissues is greater than the supply and ketone bodies are manufactured to make up the quick fuel requirement. In diabetes the amount of glucose is adequate but the glucose utilization rate is reduced below the quick fuel requirement. Ketone bodies are supplied by the liver to meet this deficit. The degree of ketosis is determined by the extent of the reduction in the glucose utilization rate. Insulin increases the glucose utilization rate in the diabetic and ketone body formation is reduced or stopped. Although glucose utilization is reduced in diabetes the depancreatized animal can utilize some glucose. Yater et al. (1933) found that the hepatectomized dog had a glucose utilization rate 56 per cent greater than when the pancreas was also removed. The impairment of glucose utilization in the diabetic is not absolute but varies with the tissue, the species and the physiological state of the animal (Drury, 1942). Insulin certainly increases this utilization, but to what extent by increasing storage of glucose and to what extent by increasing immediate oxidation is not easy to determine. Recent contributions point toward the primary action of insulin as being one of causing carbohydrate storage (Drury 1940–41; 75). Glucose utilization apparently depends upon the completion of some phase of its storage. Mirsky and his co-workers reported in 1937 (67) that the injection of very large amounts of glucose reduces and may abolish the production of ketone bodies by the liver of the depancreatized dog in the complete absence of insulin. Excessively high blood-sugar levels probably influence glucose storage to some extent in the same manner as insulin for Soskin and Levine in 1937 found that, as in the normal dog, sugar utilization also depends upon the height of the blood sugar in the completely depancreatized organism. This also occurs in the human diabetic for an excessive carbohydrate intake increases glucose utilization in most diabetics and decreases their ketosis (Mirsky, 1942).

In fitting the ketosis of diabetes into the general picture the higher degree of ketosis which may occur in this condition in comparison with fasting should be considered. One possibility is that the quick fuel demand of the fed organism is a great deal higher than in fasting and the diabetic is a fed organism while the portion (supply for the nervous system) which may be met with glucose is the same in both cases. Or the quick fuel demand in the diabetic may be much higher than in the normal subject. Of course the etiology of diabetes is still clouded with uncertainty. The insulin lack may perhaps sometimes be relative rather than absolute. The place of the diabetogenic activity of the anterior pituitary in the disease in man is still unknown. If it is an important factor diabetic ketosis, at least in its more severe degrees, may represent a pathological disturbance in a physiologic mechanism.

Several observers have reported a ketosis resulting from severe hypoglycemia due to insulin administration in diabetics as well as in the non-diabetic organism (Collip, 1923; Burn and Ling, 1928; Somogyi, 1936, 1941). This has been explained by Burn and Ling, 1928 and by Somogyi, 1941 as a result of the low liver glycogen known to follow insulin over-dosage. The ketosis appears to come toward the end of, or to follow the hypoglycemia. It may well be instituted by the reduced amount of sugar available for utilization by the tissues. The latter would be an inevitable result of the low blood sugar and the glucose lack resulting from the oxidation or irretrievable conversion to fat or other carbohydrate storage forms of the available carbohydrate by the excess insulin.

In considering ketosis as a normal physiologic mechanism even in diabetes a word should be said about the relation between diabetic

coma and ketosis. There is no evidence that the ketone bodies possess any pharmacological action so their contribution to coma must be an indirect one. Ketosis is by no means a constant accompaniment of coma (Baker, 1936) but it may contribute to its occurrence. Like many physiologic mechanisms, particularly those of an emergency character, ketosis has what at least appears to be certain undesirable characteristics. Transportation of ketone bodies by the blood ties up some of the base normally used to carry carbonic acid. At times this increases to a serious extent but there are undoubtedly other factors contributing to the severity of the acidosis in most of these cases. It would be undesirable for the organism to retain ketone bodies in large quantities and the kidney shows a threshold for them. As a result, whenever there is a ketosis, a small part of the ketone bodies produced (Crandall et al. 1940–41) is lost in the urine. They carry fixed base with them and this leads to dehydration. In diabetes, glycosuria may contribute further to dehydration and this factor appears to be an important one in the development of diabetic coma. We know that it is not the sole factor and treatment of dehydration alone will not relieve coma. It is probable that diabetic coma results from a generalized metabolic disturbance to which the ketosis contributes its part. Of course, as a practical proposition evidences of ketosis remain as useful guides in the regulation of diabetes and the prevention of coma.

SUMMARY

Ketosis is a physiologic mechanism in which a special type of fat metabolism comes into play. Ketone bodies are produced by the oxidation of fatty acids by the liver and are carried in the blood stream to the extrahepatic tissues where they are utilized as a source of energy. The transformation of fatty acids is a supplementary mechanism operating when there is a shortage of carbohydrate for fuel.

Glucose and the ketone bodies comprise a special type of energy source which has been called 'quick fuel.' Except for the nourishment of the central nervous tissue the ketone bodies appear able to supply energy in any case in which glucose is ordinarily required. The onset and extent of ketosis is dependent upon the demand for quick fuel and the shortage of glucose. This shortage may be absolute as in fasting or relative due to an inability of the tissues to utilize glucose as in diabetes.

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EDITORIALS

RELATION OF ANDROGENS TO KIDNEY FUNCTION

MANY EXPERIMENTAL endocrinologists have made the casual observation that excision of various glands or the administration of different hormone products may lead to changes in the size of the kidneys. The relationship of hormone factors to the volume and composition of urine, however, has had relatively little study except in special cases such as in myxedema or diabetes. The influence of pituitary extracts on renal functions is, of course, a well known exception to the general statement.

Among the first to investigate the influence of androgens upon the kidneys were Korenchevsky[1] and various collaborators who first reported that the administration of 'purified androgenic extracts' to rats led to an enlargement of their kidneys. Conversely, castration led to diminution of renal size, hence the expression 'castration kidneys' which these authors coined. Over the next 7 years, Korenchevsky's group extended the studies, using a variety of hormones. Androsterone as well as testosterone esters were found so regularly to produce kidney hypertrophy as to be designated 'nephrotrophic hormones.' Certain estrogens, on the other hand, were reported to produce cyst-like degenerative changes. These workers suggested that androsterone, which has weak androgenic but strong nephrotropic effects, would be worthy of clinical trial in renal disorders. Three years ago Selye[2] made a systematic restudy of the problem using mice as subjects. He found that testosterone propionate given over a period of 2 to 3 weeks caused marked enlargement of the kidneys with pronounced hypertrophy of the tubular epithelium as well as of the parietal lining of the capsules. The following year he[3] extended the observations and reported that steroid hormones rather generally produce renal enlargement. He further noted that the kidneys of testosterone-treated animals were 'functionally superior' to those of non-treated animals in that they were more resistant to nephrotoxic agents. Last year Luden and colleagues[4] studied the matter further in rats using testosterone propionate, desoxycorticosterone acerate and estradiol benzoate. They found that the first two caused genuine renal hypertrophy and that the estrogen also caused increase of kidney weight but the effect of the latter was due merely to fluid retention within the renal tissues. These authors too suggested the possible clinical utility of the findings.

The problem has recently been further studied by Welsh and collaborators.[5] They administered testosterone propionate to female dogs and studied the influence of that androgen on various renal functions. The glomerular filtration rate was determined by measuring the clearance speed of injected creatinine. The blood flow and tubular secretion rate were tested by injections of diodrast. The testosterone was given in daily doses of 100 mg. administered in oil, the total dosages ranging from 600 to 2100 mg. Renal clearances were determined in the morning before the daily androgen injections so that from 20 to 24 hours always elapsed between the administration and the renal function test.

It was found that neither the glomerular filtration rate nor the renal blood flow was significantly affected. On the other hand, the ability to excrete diodrast rose rapidly, the increases amounting in some cases to 100 per cent. At the same time the output of sodium and potassium was decreased—a result which, the authors suggest, may have been due to augmented resorption of these substances.

There seems to be no doubt now that testosterone can cause an increase in renal tubule activity. To this extent, the earlier suggestions that the androgen may be found to have significant clinical use is further supported. As Welsh points out, however, the problem will have to be studied more specifically with regard to other individual substances, since the excretion of these may be differently influenced than is that of diodrast. Furthermore, the fact that the increased tubule activity is not accompanied by increased blood flow suggests that the effect of the androgen may be something less than genuinely physiologic.

Obviously the evidence now at hand does not justify indiscriminate dosing of albuminuric pa-

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tients with androgens. The indication seems clear, however, that the possibilities of clinical usefulness of these agents should be adequately explored, utilizing at least the standard functional tests to obtain controlled data. Cases of chronic nephritis which are in a stationary status would presumably be put in little or no additional jeopardy by the conservative use of testosterone. Selye's evidence that the androgen increases the resistance to nephrotoxic agents seems especially suggestive for further investigation.

R.G.H.

PELLET IMPLANTATION OF AMINO AND PROTEIN HORMONES

With the sole exception of the oral treatment of hypothyroidism with desiccated thyroid gland, endocrine therapy, as yet, lacks the implementation necessary for providing entirely satisfactory and efficient treatment of glandular deficits. In a large measure, this is due to our inability to administer the currently available endocrine principles in such a way that levels of concentration comparable to physiologic ones are secured. The slow absorption and sustained cumulative action of orally administered desiccated thyroid result from certain pharmacologic properties of the thyroglobulin molecule; among these are *a*) the dependence of the thyroid principle for potency upon the presence of thyroxin and diiodotyrosine in thyroglobulin combination, *b*) the necessity of a similar enzymatic digestive process for the absorption of the thyroglobulin fragments across alimentary membranes and across the cell membranes of the thyroid follicles and *c*) the natural depot function of colloid from which mobilization of the active iodine-containing amino acids occurs.

This simple, oral administration is not possible with other glandular materials. Alimentary digestion and absorption do not provide a steady supply of the hormones of these other glands and oral use are not economical even when purified extracts of these, or their known active chemical compounds, are administered. When aqueous glandular extracts or solutions of hormones are injected subcutaneously or intramuscularly, the results are evanescent because of rapid absorption, rapid inactivation or elimination. Repeated and frequent injections of fractional dosages reduce the peaks of concentration and tend to prolong the effectiveness of therapy but these are a burden and discomfort to the patient. The Muirhead treatment of Addison's disease with epinephrine is an example of a heroic struggle to prolong an evanescent action.

The chemical and pharmacologic properties of the ovarian, testicular and adrenal steroids have permitted significant advances in methods for decreasing the rate of absorption and prolonging activity. Esterification of these has supplied active compounds with solubilities far lower than that of the free steroid. The employment of vegetable oils as solvents for intramuscular injections of these steroids and their esters has allowed further reduction in the rate of absorption.

The pellet implantation technic introduced by Deanesly and Parkes[1] some 5 years ago permitted the utilization of sterile, compressed tablets of steroids embedded in subfascial sites as local depots for a continuous mobilization of the active principle. The most satisfactory clinical application of the pellet technic has been that of desoxycorticosterone acetate in the treatment of Addison's disease. Testosterone and its esters have been employed by implantation with good advantage in treatment of the intrinsic testicular hypogonadism of adolescence. The normal cyclic nature of ovarian function has prevented application of the pellet technic to estrogen and progesterone therapy. In adolescent hypoövarianism of intrinsic ovarian origin, or in the so-called climacteric syndrome, pellet implantation of estrogens does not seem advised on the basis of the studies of Lipschütz[2] which indicate the likelihood that prolonged non-cyclic estrogenic therapy favors tumorigenesis.

Application of the pellet implantation technic to the amino and protein hormones, which have much higher solubilities in body fluids than do the steroids, did not seem, at first consideration, to be practical. Indeed, if prolongation of absorption were obtained, it was envisioned that enzymatic fragmentation, deaminization and other destructive changes might result. The slower absorption permitted by insulin protaminate, gelatin solution of epinephrine and vasopressin tannate has indicated that this objection was probably without foundation.

Parkes[3] of the National Institute of Medical

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[1] Deanesly, R., and A. S. Parkes: *Proc. Roy. Soc., London, s. B.* 124: 279. 1937.

[2] Lipschütz, A.: *J. Am. Med. Assoc.* 120: 171. 1942.

[3] Parkes, A. S.: *J. of Endocrinology* 3: 220. 1942.

Research of London has recently reported interesting experimental studies of pellet implantation of certain of the non-steroid hormones.

Cholesterol and benzyl sulfanilamide were chosen as excipients for the hormones, following preliminary experiments with various substances. Tablets were prepared with an ordinary hand tablet-making press. These were implanted into the flank of laboratory animals, which were usually rats.

Parkes found that tablets composed of equal amounts of cholesterol and thyroxin suffered no significant weight loss even after 167 days of implantation. More satisfactory results were secured with the use of more soluble sodium salts of thyroxin but these studies are not reported in the present communication.

Tablets composed of 15 per cent of epinephrine and 85 per cent of cholesterol were found to lose between one-quarter and one-third of their hormone content in 28 days. The data secured indicated that this absorption was quite uniform over this interval. It was found that a 100-mg. tablet containing 25 per cent of epinephrine and 75 per cent of cholesterol provided an animal with 10 mg. of epinephrine during the course of one month.

Sex differences in the response of male and female rats to the implantation of 100-mg. tablets containing 10, 15 or 25 per cent of crystalline insulin and cholesterol were encountered; this treatment was usually lethal in the male. Data secured on female rats indicated that 2 to 3 mg. of insulin was absorbed at a fairly uniform rate in the course of a month from tablets containing 25 per cent of insulin. Studies on the re-implantation of tablets which previously had been implanted for 14 days indicated that there was no inactivation of the remaining insulin.

The implantation of 100-mg. tablets composed of an extract of chorionic gonadotropin which contained 20 I.U. per mg. and 50, 75 or 90 per cent of cholesterol permitted rapid absorption of the active principle; these studies gave proof that contact of the gonadotropin with body fluids for 6 days did not inactivate it. The residue of a 100-mg. tablet containing 10 per cent of gonadotropic extract and 90 per cent of cholesterol following implantation for 6 days, was found to contain the equivalent of 0.5 mg. (10 I.U.) of gonadotropin upon assay in immature female rats.

The effect of implanting tablets containing 10 per cent of gonadotropic extract of horse or of sheep pituitary and 90 per cent of cholesterol or benzyl sulfanilamide was investigated. It was found that the implantation technic permitted uniform absorption of 10 mg. of horse pituitary gonadotropic extract over a period of 5 days. The absorption of the sheep pituitary gonadotropic extract from implanted tablets was much slower than that observed over a 5-day period in the case of the horse pituitary extract; however, a comparision of the ovarian response of immature female rats to single injections of this pituitary extract and to implant absorption indicated that the effectiveness of the extract was increased markedly, perhaps as much as 20 times, when the implantation technic was employed.

These findings of Parkes are significant and provide conclusive proof that *a*) contact with body fluids even for relatively long periods of time does not inactivate implanted epinephrine, insulin and extracts of chorionic and pituitary gonadotropins; *b*) the implantation of tablets of those non-steroid substances which contain suitable excipients provides artificial depots from which uniform and gradual absorption of the active principle may be secured; and *c*) the implantation technic, by providing a continuous flow of the hormone, permits a more efficient utilization by the individual.

The clinician will await with interest further studies designed to implement therapy with the non-steroid hormones. The work of Parkes offers particular encouragement to the physician who has attempted to use the available pituitary extracts in the treatment of his patients. A method may be provided for enhancing the action of the growth-promoting fraction of the pituitary, which has given particularly poor results in clinical practice. A continuous supply of this principle would appear to be a prerequisite for successful therapy.

The disappointments which have followed so commonly the use of chorionic and pituitary gonadotropins have been attributed by most workers to an inability to maintain constantly effective levels of these in the body fluids. A technic which accomplishes the results Parkes has secured with implanted tablets may permit the more effective clinical use of these gonadotropins. It is assumed commonly that equine gonadotropin permits a prolonged and cumulative action because the molecule is too large to pass through the kidney. Studies of the effects of implanting tablets of it may shed some light upon its clinical shortcomings. It may be found to be more effective under these circumstances.

E.C.H.

Abstracts of

CURRENT CLINICAL LITERATURE

Editor: DANIEL A. McGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

BOOK REVIEWS

DUERST, JOH. ULRICH.

Etiology of goiter. Prof. der Hygiene und Zootechnik an der vet. med. Fakultät der Universität Bern. 540 pp., 82 illus. *Medizinischer Verlag*, Hans Huber, Bern, Switzerland, 1941.

The author concludes that the thyroid and thymus glands which derive from the branchial arches continue to be of use in respiration. According to his view, goiter develops in all instances in which the CO_2 content of the air is increased; as, for instance, goiter of animals which are kept during winter in barns is caused by an increase in the CO_2 content of the air. The author bases his view on results of his own observations and on a rich literature. In the first part of the book phylogenetic considerations support the theory. The second part deals with the physiology and pathology of the thyroid and thymus. In the third part the influence of terrestrial factors are reviewed and finally the rôle of man himself, as his diet, living conditions, occupation and economic factors, are considered in the etiology of goiter.

The publisher has done well in presenting the work under wartime conditions. The reader will follow the book with interest and he will find an unusual presentation of the problem.—*R. Tyslowitz.*

W. C. HUEPER.

Occupational tumors and allied diseases. Charles C Thomas, Springfield, Illinois, 1942. Pp. 896.

This book is addressed primarily to those whose work falls in the field of industrial health. Two chapters, however, are of interest to technical endocrinologists. These are "Occupational Tumors of the Endocrine Glands" and "Occupational and Accidental Tumors of the Sex Glands." Here the reader will find a clear and concise discussion of the literature gathered from many sources, with bibliographic references.—*R.G.H.*

ADRENALS

WHARTON, G. K.

Functions of the adrenal glands. *Internat. Clin.* 2: 1. 1941.

In this résumé the author reviews much controversial literature in an attempt to appraise our present knowledge of adrenal functions. We know that the adrenal cortex has a reciprocal influence with the pituitary, thyroid, sex, and thymus glands. Electrolytic, carbohydrate, fat and vitamin-B and -C metabolisms are some of the varied functions of the cortex. The adrenal medulla has a single hormone which influences carbohydrate and muscular metabolism and the thyroid gland. The various diseases associated with changes in the adrenals are discussed.—*I.B.*

ENDOCRINE GENERAL

EDITORIAL

The humoral control of internal secretion. *J. Am. Med. Assoc.* 120: 456. 1942.

Preliminary investigations are considered by the authors to indicate a humoral control (low blood calcium) of the parathyroid glands. Such humoral control of endocrine secretion is suggestive of the homeostatic mechanism for the regulation of the blood sugar by the liver, as reported by Soskin and his co-workers in 1938, and marks an important step in the understanding of the mechanism by which physiologic change is controlled.—*C.P.*

BACH, E., AND H. WINKLER.

The potentiation of the corpus luteum hormone in the treatment of threatened and habitual abortion. *Arch. f. Gynäk.* 172: 97. 1941.

Vitamin E increased the activity of the corpus luteum hormone. A combination of both vitamin and hormone was particularly useful in the prevention of habitual and imminent abortion; 30

mg. α-tocopherol proved to be the optimal daily dosage.—*Erich Kaufmann (Biol. Absts.).*

DUSSER DE BARENNE, D., AND F. A. GIBBS.
Variations in the electroencephalogram during the menstrual cycle. *Am. J. Obst. & Gynec.* 44: 687. 1942.

Daily encephalograms of eleven healthy young women were obtained during at least one menstrual cycle. These revealed no rigid relations between the electrical activity of the cortex and the menstrual cycle. In the majority, however, electrical activity was slowed after the onset of menstruation.—*E.C.H.*

BEAN, W. B.
A note on the development of cutaneous arterial 'spiders' and palmar erythema in persons with liver disease and their development following the administration of estrogens. *Am. J. M. Sci.* 204: 251. 1942.

The development of cutaneous arterial "spiders" in 2 of 3 chronic alcohol addicts and palmar erythema in 1, following therapy with potent estrogens suggested to the authors that these stigmata of liver disease, pregnancy and deficiency diseases may result from abnormal metabolism of the 17-ketosteroid hormones.—*C.P.*

BEASER, S. B., AND T. B. MASSELL.
Therapeutic evaluation of testosterone in peripheral vascular disease. *New England J. Med.* 227: 43. 1942.

Measurement of a patient's ability to walk on a level surface at a given rate until the onset of claudication is a satisfactory method of evaluating peripheral circulatory function in ambulatory patients. Testosterone propionate in doses up to 150 mg. per week did not prevent intermittent claudication in the lower limbs of 6 patients with occlusive vascular disease.—*Authors' Abst.*

BICKENBACH, W.
The gonadotropic hormone of the placenta. *Arch. f. Gynäk.* 172: 152. 1941.

On extraction of the placenta a maximum of gonadotropic hormone was found 2 to 3 months from the onset of pregnancy, in accordance with its simultaneously high level in urine and blood. At the height of the hormone formation 100 m.u. were extracted from 1 gm. of tissue; this is taken to prove the placental origin.—*Erich Kaufmann (Biol. Absts.).*

BLOTNER, H.
The amount of iodine in the blood and urine in patients with diabetes insipidus. *Am. J. M. Sci.* 203: 708. 1942.

Fifteen patients were studied; in addition the thyroids of 2 were examined following total thyroidectomy. In patients untreated and showing marked polydipsia and polyuria the average blood I was 5.6 gamma % (range 3.0 to 12.6). The average 24-hour urinary excretion was 0.319 mg. (range 0.028 to 0.936 mg.). Following pituitrin administration the average blood I was 9.4 gamma % (range 4.2 to 17.6 gamma %), and the average 24-hour urinary excretion was 0.189 mg. (range 0.078 to 0.466 mg.). The relation of organic to inorganic blood I was considered practically normal in these cases. The I content of the 2 thyroid glands was decreased as compared with that of two control glands. The findings may indicate a failure of absorption of I by the kidney in diabetes insipidus, a failure which is corrected by pituitrin administration.—*Author's Abst.*

BUCHER, C. S.
The use of anterior pituitary extract in the treatment of allergy. *Illinois M. J.* 82: 202. 1942.

Anterior pituitary extract equivalent to 18.5 gm. of fresh gland was administered subcutaneously daily for 7 to 10 days, thereafter twice weekly and later once weekly. An average of 25 injections was required, with individual differences. Permanence of freedom from symptoms lasted for several months to several years. A second treatment necessitated by return of symptoms required much less extract. In 300 cases over a 11-year period the approximate % of results were: good results, 82% (70 to 100% symptomatic relief), fair results, 12% (less than 70% relief), and little or no relief, 6%.—L. N. Wolf (*Biol. Absts.*).

BUÑO, W., AND O. F. GROSSO.
Fibroadenoma of the mammary gland in the female and estrogens. Arch. clín. inst. endocrinol. (Montevideo) *1, 1:* 305 (1937–40).

A young female treated for acne for a prolonged period with estradiol benzoate by inunction developed bilateral fibrous adenomas. The unaffected part of the gland proved on examination to be in the stage of active proliferation. The relation between treatment with estrogen and tumor formation in this case is suggestive although not conclusive.—*A.E.M.*

FRANK, I. L., AND S. H. GEIST.
Postmenopausal endometriosis. A case report and review of the literature. *Am. J. Obst. & Gynec.* 44: 652. 1942.

Clinical and endocrine studies are reported upon a 63 year old patient with endometriosis. A series of 203 cases of endometriosis, 23 of which occurred postmenopausally, is presented.

The authors conclude that, while endometriosis is present not infrequently in postmenopausal women, the lesions are in a state of regression and atrophy and are incapable of renewed growth activity. No evidence was encountered that endometriosis originates *de novo* during the climacteric.—*E.C.H.*

GIBBS, F. A., AND D. E. REID.
The electroencephalogram in pregnancy. *Am. J. Obst. & Gynec.* 44: 672. 1942.

Encephalographic study of 28 pregnant women, 8 of whom had toxemia, indicates that the electrical activity of the cortex is slowed during pregnancy and that patients with toxemia generally show more high-voltage fast activity and less normal activity than non-toxemic patients. —*E.C.H.*

GREENBLATT, R. B., F. MORTARA AND R. TORPIN.
Sexual libido in the female. *Am. J. Obst. & Gynec.* 44: 658. 1942.

The effects upon libido of 55 women, who received pellet implants of testosterone propionate (total amounts 25 to 400 mg.) and of 16 women treated by implants of progesterone pellets are reported.

The authors speak of the rôle of the hormones in influencing libido as "a test tube chemical equation": progesterone may be administered to depress excessive libido; androgens increase deficient libido. They entertained no fear of virilization phenomena from the dosage levels of androgens employed.

The authors conclude that "the psychotic tendencies of the nymphomaniac, the neuroses and unhappiness of the frigid female, and the problems of the incompatible couple, with their sociologic implications, are amenable to hormone therapy."—*E.C.H.*

GUTTMACHER, A. F.
The rôle of artificial insemination in the treatment of sterility. *J. Am. Med. Assoc.* 120: 442. 1942.

The subject of artificial insemination is masterfully and adroitly handled by Guttmacher by repeated reference to the great accomplishments in this field in veterinary medicine. The indications in man are: A. Mechanical defects (hypospadias, impotence, vaginismus, etc.), B. Chronic sterility due to pathology of the female genitalia, and C. Cases where the husband is sterile but the female is apparently fertile. The accepted technique is the intravaginal or intracervical deposition of semen. The intrauterine deposition does not give as good results. In 27 cases of group C, 17 pregnancies resulted while several attempts in 7 cases failed to produce pregnancy. Insemination with spermatozoa collected by aspiration or operation from the epididymus or testes has not been tried sufficiently to estimate the degree of success. The date for insemination is carefully selected on the basis of the menstrual period. In a 28 day cycle days 11 and 15 are tried the first month, days 10 and 14 the second month and days 12 and 16 the third month. This procedure may have to be repeated varying the days back and forth within the fertile period. The moral and legal aspects and precautions are also listed.—*C.P.*

KASSELBERG, L. A.
Exfoliative dermatitis due to diethylstilbestrol. *J. Am. Med. Assoc.* 120: 117. 1942.

A single case history is presented in which a menopausal patient developed exfoliative dermatitis after two weekly doses of 1 mg. diethylstilbestrol intramuscularly. Scratch tests were violently positive with diethylstilbestrol and negative for the vehicle sesame oil. A patch test was negative.—*C.P.*

KOSMAK, G. W.
Gynecologic and other implications which relate to an aging female population. *Am. J. Obst. & Gynec.* 44: 897. 1942.

A special article, which considers various aspects of gynecic gerontology. Among the subjects discussed are: nutrition and metabolism; alterations in the nervous, digestive, urinary and reproductive systems; alterations in other organs and systems; and operations upon older women. The fact is stressed that the hormonal changes of the climacteric have received one-sided attention as compared with that accorded vascular changes, nutritional problems and the psychologic aspects of advancing years. The author points out the necessity for a new line of medical thought and approach to avoid relegating 'the increasing

numbers of our people to a domain of despair and uselessness.'—*E.C.H.*

LEBLOND, C. P.
Detoxification of progesterone derivatives in the liver. *Am. J. M. Sci.* 204: 566. 1942.

The author found by study in the 75% hepatectomized rat that free pregnanediol is detoxified in the liver since these hepatectomized animals had a greater degree of anesthesia than did the controls. Similar experiments with pregnanediol and pregnanedione indicate that their detoxification is not due to storage in the liver or excretion in the bile but rather to an inactivation by the liver cells.—*C.P.*

MANARO, J. M., A. ALBRIEUX AND H. ALVAREZ.
The value of determinations of gonadotropic hormone in the urine in a case of mole and chorionepithelioma. Arch. clín. inst. endocrinol. (Montevideo) *1, I:* 567 (1937–40).

The case reported showed relatively small elimination of gonadotropic hormone (about 100,000 rat units per liter) at the time of operation, but after 4 and 5 months the titer was still over 5000 units. However clinical signs did not support the supposition of a metastasis. Five months later the gonadotropic content had fallen to between 20 and 100 units. The necessity for repetition of the postoperative tests and the taking into account of the clinical picture in making diagnosis is emphasized.—*A.E.M.*

MASON, L. W.
Spontaneous abortion and its treatment with progesterone. *Am. J. Obst. & Gynec.* 44: 630. 1942.

Thirty of 34 patients with 'threatening' abortion treated with progesterone went to term. Fifteen of 17 patients with histories of recurrent abortion who were treated with progesterone went to term. Usual dosage was 5 mg. three times a week; dosages were reduced after the fourth month. Good prenatal care is considered an integral part of an antiabortional regime.—*E.C.H.*

MENGERT, W. F., AND W. D. PAUL.
Artificial pyrexia in four pregnant women. *Am. J. Obst. & Gynec.* 44: 702. 1942.

Four women in the second and third trimesters of pregnancy were treated by artificial induction of fever without observable damage to the fetus in its subsequent intrauterine or early postnatal development.—*E.C.H.*

MUSSIO-FOURNIER, J. C., J. M. MANARO AND A. ALBRIEUX.
Clinical use of lactogenic hormone. *Arch. clín. inst. endocrinol.* (Montevideo) *1, I:* 575 (1937–40).

Lactogenic hormone used to increase lactation is efficacious if given early and in large doses (200 to 300 mg. total) and if the mammary tissue is sufficiently developed. The material is given in 10 doses intramuscularly and produces no distressing symptoms. For maintenance smaller doses are sufficient. If the treatment is discontinued, resumption may cause allergic reactions. —*A.E.M.*

PHILLIPS, E. W.
Allergic shock caused by synapoidin. *Am. J. Obst. & Gynec.* 44: 706. 1942.

The case of a patient who became hypersensitive to synapoidin after 17 days of therapeutic exposure is reported. Ten days intervened between the third eventful injection and the fourth which produced shock. It is suggested that the diluted material, 0.02 cc. of a 1:5 dilution, be used as an intradermal test, when a week or more has elapsed since a preceding injection.—*E.C.H.*

PRIDE, C. B., AND M. P. RUCKER.
Eclampsia and ovarian pregnancy. *Am. J. Obst. & Gynec.* 44: 575. 1942.

What is considered to be the first reported case of eclampsia associated with an ovarian pregnancy is described.—*E.C.H.*

PULVER, M., AND L. B. POSNER.
The colostrum test for pregnancy in a prenatal clinic. *Am. J. Obst. & Gynec.* 44: 690. 1942.

The method of Falls and co-workers (Am. J. Obst. & Gynec. 41: 431. 1941) was followed as regards important details. Two hundred twenty patients were tested.

The following conclusions were drawn: 1) a negative reaction is 97.4% accurate in diagnosing actual pregnancy; 2) a positive reaction is 75% incorrect in the diagnosis of non-pregnancy; 3) in pregnant women a correct reaction was obtained in 94% of cases; 4) in non-pregnant women the test was 56% incorrect.—*E.C.H.*

RAKOFF, A. E.
The diagnostic value of hormone assays. *Med. Clin. N. America* 26: 1915. 1942.

Much of the progress which has been made in clinical endocrinology during the last decade has

resulted from the demonstration of various hormones in the body fluids and the correlation of these findings with the clinical picture. Where such studies are available they frequently yield information valuable to etiological and therapeutic deductions. The author discusses the normal and abnormal relations of the gonadotropic hormones, the estrogens, androgens, 17-ketosteroids and the assay of ketosteroids, in relation to adrenal cortical disturbance, menstrual and ovarian abnormalities and other conditions. This contribution must be read in its entirety to be fully appreciated.—*I.B.*

SCHMIDT, P. P. H.

A thousand years of estrin therapy. *Lancet* 243: 84. 1942.

Zondek is credited with the discovery that the urine of pregnant mares and stallions is one of the richest sources of estrin, but Schmidt has unearthed from ancient manuscripts the interesting fact that a Persian court physician, Haly ben Abbas, who died in 994 A.D., used evaporated horse's urine for inducing stillbirth. His medical work, "The Royal Book," was translated into Latin in 1080 and went through a series of editions, the principle ones being the Venetian in 1492 and the Lyon in 1529. It was the leading medical treatise until superseded by that of the Arabian physician, Ibn Sina (Avicenna), 980–1037.—*J. B. Paton* (*Biol. Absts.*).

SOULE, S. D.

Estrogen-withdrawal bleeding. A study of the comparative activity of various estrogens. *J. Obst. & Gynec.* 44: 684. 1942.

The studies reported were done on a surgically castrated woman. Estrogen-withdrawal bleeding was employed as an index of the patient's response. Various estrogens were given orally: diethylstilbestrol, estriol, alpha estradiol and ethinyl estradiol. Alpha estradiol in propylene glycol was administered sublingually. Ethinyl estradiol was judged to be the most active estrogen employed. Alpha estradiol and diethylstilbestrol, when administered orally were found to have about equal potency when given in comparable dosages.—*E.C.H.*

SULLIVAN, C. L., AND R. J. HEFFERNAN.

Convulsions following the intravenous administration of pituitary extract. *Am. J. Obst. & Gynec.* 44: 675. 1942.

The case of a non-toxic, 37 year old primigravida who had postpartum convulsions following the intravenous administration of 3 minims of a posterior pituitary oxytocic extract is reported and the literature is reviewed.—*E.C.H.*

TAYLOR, H. C.

Relationship of the hormones to the toxemias of pregnancy. *J. Am. Med. Assoc.* 120: 595. 1942.

Since the hormones establish the altered physiology of pregnancy they may be unduly altered in abnormal pregnancy or eclampsia. The author discusses the data in favor of an imbalance of the estrogens, progesterone, and chorionic gonadotropin. The possibility of toxic products resulting from abnormal metabolism of these hormones is also considered. Other possibilities referred to are (a) Excessive quantities of antidiuretic and vasopressor hormones from the posterior pituitary, (b) Alteration in the histology and function of the anterior pituitary, (c) Adrenal insufficiency or imbalance, (d) Hypothyroidism.—*C.P.*

TRAUT, H. F.

Use and abuses of radiation therapy in obstetrics and gynecology. *Am. J. Obst. & Gynec.* 44: 638. 1942.

This general article discusses radiation therapy during these four age spans of woman: 1) the pre- and postpubertal period; 2) the reproductive period of life; 3) pre- and postmenopausal period; and 4) senescence.

The author condemns the use of 'stimulating' or 'temporary castrating' doses of radium and x-ray in the young woman. These are described as often being ineffectual or as doing permanent harm. The concensus is that no 'stimulating' effects of radiation therapy on the ovary have been established. The use of stimulating x-ray therapy for the treatment of sterility is condemned. Castration by radiation may be a conservative procedure in a young woman with grave endometriosis or mammary carcinoma. Production of abortion by x-ray therapy is held to be hazardous to future ovarian function.—*E.C.H.*

WEIL, A. A.

Acute cardio-vascular collapse after insulin shock treatment. *J. Nerv. & Ment. Dis.* 96: 556. 1942.

The relevant literature is reviewed and a case is reported of a healthy 20-year-old man in which

the patient suffered a severe collapse as a delayed reaction to insulin after he had been relieved of his hypoglycemic symptoms by the use of glucose and sucrose. The patient responded well to intracardiac injections of adrenalin. The total evidence suggests that the period immediately after recovery from hypoglycemia in non-diabetics is one of special cardiovascular vulnerability. Pulmonary edema is another danger.—*R.G.H.*

GONADS

BICKERS, W.

Puerperal uterine contractions. *Am. J. Obst. & Gynec.* 44: 581. 1942.

Uterine contractions of six normal primiparous women following term deliveries were studied by an intrauterine balloon method. Spontaneous and pituitrin-induced uterine contractions were observed to decrease rapidly during the first ten days of puerperium. Estrogen administration enhanced uterine motility. It is suggested that estrogen, in addition to pituitrin, should be used in the treatment of puerperal hemorrhage occurring after the fifth day.—*E.C.H.*

BROWN, W. E.

Treatment of gonorrheal vulvovaginitis with estrogens. *Am. J. Dis. Child.* 64: 221. 1942.

Treatment of gonorrheal vulvovaginitis with estrogens depends for its success upon maintenance of a cornified vaginal epithelium. Many of the alleged failures of estrogen therapy have been due to lack of cornification. The authors recommend use of vaginal smears for the control of estrogen dosage and they introduce 'physiologic units' rather than the usual biologic units. The physiologic unit is the amount of estrogen necessary to cornify the vaginal epithelium of the patient. Case reports illustrating the various causes of failure in estrogen therapy in gonorrheal vulvovaginitis are included and discussed.—*Author's Abst.*

CERVIÑO, JOSÉ MANUEL.

Adiposity with transitory hypogenitalism in prepuberty and adolescence. Arch. clín. inst. endocrinol. (Montevideo) *1, I:* 289 (1937–40).

A group of cases of juvenile adiposity show clinical signs of Froehlich's syndrome except that the abnormality is not permanent. Height is greater than normal and occasionally a true gynecomastia is observed. The B.M.R. is frequently lowered without signs of thyroid involvement and with high resistance to thyroid medication. This syndrome may be encountered in boys who later develop pubertas praecox with hypergenitalism. The obesity in a second group is more of a general type. The bone and muscular development is exaggerated, puberty begins at an early age and there may be a tendency towards hyperglycemia. A third large group presents intermediates between the two types. The treatment consisted essentially in diet with or without thyroid medication.—*A.E.M.*

CLARKE, E., AND HANS SELYE

The action of steroid compounds on the vaginal epithelium of the rat. *Am. J. M. Sci.* 204: 401. 1942.

A series of 49 new steroid compounds including their control compounds testosterone and progesterone were studied for vaginal effect in ovariectomized or immature rats. All hormonally active steroids, whether folliculoids, luteoids, corticoids, or testoids, stimulate the vaginal epithelium to undergo stratification, cornification and mucification. While cornification is the most common type of response to estrone, mucification is more frequently seen following treatment with androstane and 17 substituted androstane derivatives. All etiocholane and 17 substituted etiocholane derivatives proved inactive unless the C_5 hydrogen was removed by the presence of a Δ^4 or Δ^5 double bond. On the basis of their observations they believe that local factors determine the type of vaginal response but that epithelium proliferation accompanies the action of all steroid hormones.—*C.P.*

ENGELHART, E., AND P. SCHRANK.

Experimental studies on the behavior of uterine muscle following orally active corpus luteum hormone. *Arch. f. Gynäk.* 172: 110. 1941.

The contracting effect of injections of extracts of posterior pituitary lobe was inhibited in mature female rabbits by feeding of 5 mg. pregnenolone. A 50 times greater dose produced decidual changes in the uterine mucosa of castrated women.—*Erich Kaufmann* (*Biol Absts.*).

ENGELHART, E., AND P. SCHRANK.

Experimental studies on the effect of male sex hormone (testosterone propionate) upon the uterus. *Arch. f. Gynäk.* 172: 129. 1941.

The action of the posterior pituitary lobe upon the uterus of female rabbits was inhibited by 10

mg. testosterone propionate and 50 mg. caused secretory changes, but in castrate women no alteration of the mucosa and no influence upon amenorrhea was demonstrated.—*Erich Kaufmann (Biol. Absts.).*

HAMILTON, JAMES B.

Male hormone stimulation is prerequisite and an incitant in common baldness. *Am. J. Anat.* 71: 1942.

The etiology of common baldness was studied experimentally in men with testicular insufficiency, namely: 10 eunuchoids; 94 eunuchs, 10 of whom had been castrated prepubertally, 34 bilaterally orchidectomized during adolescence, and 50 castrated as adults.

Common baldness never appeared in the 54 men who did not mature sexually. This is scarcely fortuitous in view of the (a) genetic predisposition to alopecia in some of these men as indicated by tendencies to become bald when provided with exogenous androgens and by the prevalence of baldness among normal male relatives: (b) high incidence of some hair loss in normal men, 43% according to Snyder and Yingling. Concomitantly, the amounts of dandruff and sebaceous secretion were less in castrates than in normal men. Male hormone treatment of 12 of these castrate and eunuchoid men, providing stimulation considered equivalent to that in normal men, resulted in increased sebaceous secretions, acne and dandruff, and 4 instances of baldness in a pattern observed in normal men. Progressive loss of head hair ceased when androgenic medication was discontinued in 2 cases, recommenced upon further therapy. Castration of men becoming bald prevented progression of alopecia but promoted no general regrowth of hair on bald areas. Pedigrees of patients receiving testosterone compounds suggest that a genetic predisposition and male hormone stimulation are necessary to development of common baldness.—*Courtesy Wistar Advance Abstracts.*

HECKEL, G. P.

The estrogen sparing effect of hysterectomy. *Surg., Gynec. & Obst.* 75: 379. 1942.

Fourteen pseudopregnant rabbits underwent varying degrees of subtotal hysterectomy, following which the corpora lutea were maintained as indicated by the reaction to pituitrin of the uterine muscle. The degree of prolongation was proportionate to the amount of tissue removed. With 25 pseudopregnant rabbits some with uterus intact, the others with varying degrees of uterine removal, it was demonstrated that amounts of estrogen inadequate to maintain the corpora lutea in the intact animal were sufficient to prolong their span in partially hysterectomized animals. In 5 animals rendered pseudopregnant twice in succession an amount of estrogen insufficient to prolong the corpora of the first pseudopregnancy did so with a second, providing subtotal hysterectomy had been carried out. Relief from climacteric symptoms following partial hysterectomy in a 44-year-old woman was observed. It is suggested that hypoplastic uteri are associated with relative hyperestrinism due to the sparing of estrogenic hormone, thus suppressing the pituitary gonadotropin.—*Robert Lyon (Biol. Absts.).*

HUNDLEY, J. M., W. K. DIEHL AND E. S. DIGGS.

Hormonal influences upon the ureter. *Am. J. Obst. & Gynec.* 44: 858. 1942.

The authors report studies designed to establish hormonal grounds for two sets of striking alterations which occur in the ureters during pregnancy: 1) a marked hypertrophy of the musculature, especially at its lower end (the sheath of Waldeyer); and 2) the relative atony, i.e., cessation of ureteral peristalsis, which occurs as pregnancy advances. Observations with Trattner's hydrophorograph upon 130 normal pregnant women indicated that, during the first trimester, the peristaltic behavior of the ureter was similar to that of the uterus. However, there occurred with advancing pregnancy a progressive hypotonia which resulted in complete antonia from the seventh month until a short time before labor, when there is a return of peristaltic activity. Hydrophorographic studies of ureters of women receiving estrogen and progesterone therapy, indicated that estrogens stimulate ureteral peristalsis whereas progesterone allays ureteral activity. The authors state that muscular hypertrophy of the ureters, similar to that seen in pregnancy, has been observed in a male dying from a teratoma of the testis with metastatic chorionepithelioma.—*E.C.H.*

LIPSCHÜTZ, ALEXANDER.

Experimental fibroids and the antifibromatogenic action of steroid hormones. *J. Am. Med. Assoc.* 120: 171. 1942.

The author presents evidence that in the guinea pig progesterone is the most potent antifibromatogenic of the naturally occurring steroids.

Whether it will also be antifibromatogenic in the human and whether desoxycorticosterone may be more antitumorigenic, remains to be seen.—*C.P.*

McGAVACK, THOMAS H.

The estrogen-like action of desoxycorticosterone acetate upon the altered electrocardiogram seen in various hypo-ovarian states. *Am. J. M. Sci.* 204: 41. 1942.

Six hypo-ovarian females with accompanying hypo-ovarian electrocardiographic changes were treated with ovarian follicular hormone and desoxycorticosterone acetate. In all six patients the electrocardiographic changes reverted to normal with adequate therapy. The authors postulate that this effect could be produced in any one of many ways, namely, by action on the blood vessels, the blood or tissue electrolytes, or indirectly through other endocrines.—*C.P.*

RUTHERFORD, R. N.

Changes in the female genital tract during the puerperium induced by sex hormone therapy. *Am. J. Obst. & Gynec.* 44: 595. 1942.

Thirty-six women were studied during the first twelve days of the immediate puerperium by endometrial biopsies and vaginal smears. Twelve were untreated. Twelve received orally and daily 10 mg. of diethylstilbestrol for twelve days. Twelve were given orally and daily 10 mg. of methyl testosterone for twelve days. It was observed that involution was delayed by the estrogen therapy but not by androgen treatment. Repair was hastened by estrogen but retarded by androgen. Regeneration of surface epithelium was hastened by estrogen but stromal regeneration was delayed. All regeneration was delayed by androgen.—*E.C.H.*

SMITH, G. V. S., O. W. SMITH AND S. SCHILLER.

Clinical experiments in relation to the excretion of the estrogens. II. Functional flowing. Urinary estrogens before, during and after progesterone, estriol and cyclic administration of progesterone and estradiol benzoate. *Am. J. Obst. & Gynec.* 44: 606. 1942.

Observations during a 16 months' span are reported upon a patient with functional irregularities of flowing who had been under study and therapy for eight years. During the time covered by this report, large amounts of progesterone were given twice to control profuse flowing, estriol was administered orally for three months to inhibit ovarian activity and seven series of progesterone and estradiol benzoate injections were given cyclically in the hopes of establishing spontaneous and regular ovulatory cycles. This latter aim was accomplished.

Studies of urinary estrogen metabolites during this period of observation led to these conclusions: 1) functional flowing is associated with a progestin deficient metabolism of estrogens and results from the absence of adequate luteal control of ovarian function; 2) progesterone, when given in large amounts, acts specifically to induce more normal estrogen metabolism and to control bleeding; 3) estriol is comparatively ineffective in influencing pituitary-ovarian activity; 4) estrogen and progesterone withdrawal results not only in normal endometrial bleeding but in a sudden increase in the rate of estrogen destruction which is envisioned as possibly providing a necessary stimulus for normal growth and maturation of ovarian follicles; and 5) if this stimulus is supplied artificially at monthly intervals, a normal pituitary-ovarian cycle may be established which may continue after cessation of cyclic therapy.—*E.C.H.*

TORPIN, R., E. PUND AND W. J. PEEPLES.

The etiologic and pathologic factors in a series of 1741 fibromyomas of the uterus. *Am. J. Obst. & Gynec.* 44: 569. 1942.

In those cases wherein pertinent endometrial studies were made, no evidence was encountered of a significant association of hyperestrogenic endometria with fibromyomata.—*E.C.H.*

HYPOPHYSIS

ALPERS, B. J.

Diagnosis and treatment of pituitary tumors. *Med. Clin. N. America* 26: 1679. 1942.

Primary tumors of the pituitary gland may be defined as those tumors arising from the gland structures and growing within the sella turcica. This excludes, therefore, all tumors arising above the sella turcica (suprasellar) and those lying adjacent to the sella (parasellar). The occurrence of primary tumors of the pituitary varies from 13 to 15 per cent of all types of brain tumor, and probably is closer to the former figure. An incidence of 17.8 per cent is found in Cushing's series, but this is higher than found in other clinics. The tumors occupying the pituitary region are made up of the following types: (1) adenomas,

(2) hypophyseal stalk tumors, (3) cysts of Rathke's cleft. They arise, therefore, from the substance of the gland, exclusively the anterior lobe portion, from the intermediate portion, and from cells which lie along the infundibular stalk. No known tumors arise from the posterior lobe of the gland. The vast majority of the primary pituitary tumors are adenomas; the hypophyseal stalk tumors and Rathke cleft cyst represent rare primary types. The crucial problem in both the diagnosis and treatment of pituitary tumors is that of vision. The complaint of blurring or failing vision of gradual onset should arouse the suspicion of a pituitary tumor especially if there is a history of long standing headache, chronic menstrual disturbances, or loss of libido in a young adult or in an older person. Such a suspicion should lead to an ophthalmoscopic examination for the presence of optic atrophy, visual studies for hemianopsia, and roentgen examination of the skull for enlargement of the sella turcica. In a typical case, optic atrophy, bitemporal hemianopsia, and a characteristic enlargement of the sella turcica will be found. The diagnosis in such a case is usually not difficult. The differential diagnosis of pituitary tumors is not difficult. There are few conditions which simulate the complete syndrome. There are many conditions which produce optic atrophy but few which cause optic atrophy and bitemporal hemianopsia. None of these conditions are associated with the typical sellar deformity of the pituitary tumor. The hypophyseal stalk tumor may be associated with sellar destruction which may rarely simulate an intrasellar tumor. It is difficult to establish set rules concerning the use of surgery or irradiation in the treatment of pituitary adenomas. In cases with definite optic atrophy and clear evidences of pressure on the optic nerves and chiasm, operation is preferable in order to relieve the compression already existent and to prevent further compression and hence greater visual loss. Roentgen therapy is best reserved for the following types of cases: 1. Early cases: (a) Cases with no optic atrophy, but with hemianopsia, with little or no loss of visual acuity. (b) Cases with early optic atrophy with hemianopsia, but with normal, or near normal, visual acuity. 2. Postoperative treatment. 3. Cases in which operation is refused. When irradiation is used, it should be followed carefully for its effect on the optic nerve, visual fields, and visual acuity. Any indication of advance in any of these factors should mean substitution of operation for roentgen therapy in order to preserve vision.—*I.B.*

CERVIÑO, JOSÉ MANUEL, AND CARLOS PÉREZ DEL CASTILLO.

Growth hormone in the treatment of infantile hypopituitarism with severe delay in growth. *Arch. clín. inst. endocrinol.* (*Montevideo*) *1*, *1*: 311 (1937–40).

Growth hormone given in doses of 10 to 15 cc. weekly for 6 to 12 months to 15 patients of 8 to 17 years with delayed growth on pituitary basis showed no influence on the body size although the general health was improved. Five infants of 14 to 22 months' age, showing retarded growth, including a pair of twins and a mongolian patient responded satisfactorily in growth as in general development, but developed some digestive disturbances. On cessation of treatment both the digestive symptoms and the growth subsided.—*A.E.M.*

DIECKMANN, W. J., AND M. S. KHARASCH.

Solution of posterior pituitary sulfonate (pit sulfonate) in labor. *Am. J. Obst. & Gynec.* 44: 820. 1942.

In order to favor slower absorption, the authors prepared a sulfonate by precipitation of posterior pituitary principles from aqueous solution with anthraquinone 2.6 disulfonic acid and by suspension in a 0.5 per cent solution of sodium-anthraquinone 2.6 disulfonic acid. Clinical studies are reported, which indicate that the sulfonate is absorbed more slowly and has a more prolonged action than stock aqueous solutions. These studies have included: treatment of diabetes insipidus; investigations of uterine contractions induced in pregnancy (intra-uterine bag, capicographic, Lorand tocographic and Fenning hysterographic methods); observations upon contractility of the postpartum uterus; and attempts at induction of labor. These latter observations are held to warrant the belief that the sulfonate can be used with less danger to the mother and child than the stock aqueous solution. The authors conclude that the effects of the sulfonate when used at term are characterized by a longer latent period, less likelihood of tetany and longer duration than those of usual solutions of posterior pituitary.—*E.C.H.*

DYNES, J. B.

Calcified pituitary tumor with myxedema, episodic hyperthermia and stupor. *The Lahey Clinic Bulletin* 3: 39. 1942.

A long-standing, advanced case of pituitary adenoma is described in which a large calcified

mass was disclosed by x-rays in the sella turcica region. The patient at 53 presented a history of failure of puberal development, episodic attacks of hyperthermia and stupor for 24 years and signs of "fugitive acromegaly." In addition to numerous pressure symptoms, there were disclosed anemia; hypogenitalism with absence of hair on the face, trunk and extremities; myxedema with elevated blood cholesterol, low basal metabolic rate, dry skin, slow pulse and sensitivity to cold despite the taking of 5 grains of thyroid daily; and positive water balance in an adrenal-cortex function test. The case seemed hopeless for adequate therapy but the thyroid was reduced to 1 or 2 grains daily to forestall possible Addisonian crises and NaCl was given 5 or 6 gm. daily. On this treatment the patient reported himself as stronger and more energetic.—*R.G.H.*

GROFF, R. A.

Indications for surgical treatment of pituitary tumors. *Med. Clin. N. America* 26: 1697. 1942.

The successful treatment of all malignant tumors depends upon early diagnosis. This is particularly true in brain tumors where the conservative removal of tissue is so important. Pituitary tumors, although they are not classified as true brain tumors, must be considered malignant because they can not, in most instances, be removed completely and because they press upon vital structures when they become large. Early diagnosis of the presence of these tumors prevents harmful pressure upon vital structures. Likewise, it paves the way to restoration of the normal function of the pituitary gland. Preservation of vision is the keynote of therapy in all pituitary lesions. The next important consideration in treatment is to determine whether the patient should be treated by x-ray or immediate surgery. Within the past 6 or more years it has been found that x-ray therapy is effective in diminishing the size of the solid pituitary tumors. This therapy has no effect on those tumors which have undergone cystic degeneration or upon the hypophyseal stalk tumor before it has been operated upon. The plan of therapeutic management of chromophobe and chromophile adenomas is to use x-ray therapy whenever possible as the only form of therapy. When the diagnosis is made early no hesitancy in the use of x-ray need be entertained. By early diagnosis is meant that the visual loss and the visual field defects are not marked. When visual disturbances are marked, or there is any suggestion in the historical data that the progress of the disease has been rapid, surgery should take preference over x-ray therapy. X-ray therapy in the treatment of patients with a chromophobe or chromophile adenoma demands close coöperation of the patient and weekly visual field and visual acuity examinations by the ophthalmologist. Should the visual field after this treatment fail to show any response, the treatment should be stopped and surgery be performed as soon as possible. X-ray therapy of basophilic adenoma has proven most effectual in controlling this tumor. Since visual symptoms and signs are absent in the patient, the criterion for improvement is based on the clinical course. The radiologist and clinician decide upon the amount and number of courses of therapy. Hypophyseal stalk tumors do not respond to x-ray therapy if given before operation. Since the signs and symptoms are produced by pressure upon vital structures, operation should be performed as soon as the diagnosis is made. The postoperative management of the patients should include a complete course of x-ray therapy from 2 to 4 weeks after the operation.—*I.B.*

HART, J. F., AND M. MAGIDAY.

Blood sugar in a case of complete hypophysectomy. *Arch. Int. Med.* 68: 893. 1941.

Blood sugar studies were made on a man, 36 years old, who had his hyppophysis removed five years previously in the process of excising a meningioma. To establish the fact that the pituitary body was completely eliminated detailed reports of the operative procedures and the pathologists findings are incorporated in the article. By means of sugar tolerance tests it was found that total removal of the pituitary lowers the fasting blood sugar to a hypoglycemic level without shock and gives a delayed sugar tolerance curve which may be at times a plateau. Furthermore, it was noted that the blood sugar level is not wholly dependent on the presence of this gland but that the gland functions as a blood sugar level-raising mechanism. Finally because the patient continues to live for years after the operation the gland cannot have complete control over any vital function.—*Author's Abst.*

E. J. KRAUS.

Sarcoidosis (Boeck-Besner-Schaumann disease) as cause of a pituitary syndrome. *J. Lab. & Clin. Med.* 28: 140. 1942.

A case of sarcoidosis involving the pituitary stalk and infundibulum is described. The patient's history indicated that she had been nor-

mal up to the age of 17 years. The disease developed with progressive symptoms over a period of 14 years during which time she developed diabetes insipidus, cessation of menses, atrophy of ovaries, uterus, tubes, external genitalia, and breasts; atrophy of the thyroid and adrenal glands. Terminally there was generalized emaciation including osteoporosis. At autopsy a chromophobe adenoma of the pituitary gland was found together with the sarcoidosis. It was interpreted as compensatory hypertrophy of an atrophic gland.—*B.B.R.*

PANCREAS

COLWELL, A. R.

Observed course of diabetes mellitus and inferences concerning its origin and progress. *Arch. Int. Med.* 70: 523. 1942.

If one employs the amount of insulin required daily for uniform control as a gage of the severity of diabetes mellitus in groups of patients of different ages and at different stages of the disease, the following interpretations appear to be justified: 1. Diabetes is inherent and begins at birth. 2. Before it is recognized in clinical practice it progresses through a stage the magnitude of which is fully as great as that of the known diabetes which follows recognition. 3. The rate of its progress is indicated by the age at which it is recognized. The earlier it appears, the more rapidly it progresses. It is probably more nearly correct to say the more rapidly it progresses through its unrecognized stage the earlier in life it appears. 4. During the first few years after its recognition it tends to improve temporarily, probably as a result of treatment. This improvement does not affect its subsequent course. 5. After some 10 years of known existence there are indications that it may show progressive and permanent improvement. 6. These rules frequently appear to be violated in aged persons with diabetes, probably because of chronic complications. *Author's summary.—I.B.*

DEWEES, E. J., AND P. H. LANGNER.

Non-diabetic glycosuria. A follow-up study with glucose tolerance tests. *Am. J. M. Sci.* 204: 491. 1942.

Of thirty-seven individuals with apparent non-diabetic glycosuria as determined by a single glucose tolerance curve 5 to 13 years ago, a greater number developed diabetes than can be accounted for on the basis of chance. The degree of glycosuria was of no prognostic value. Proven non-diabetic glycosuria appears to be non-detrimental to health.—*C.P.*

EISELE, H. E.

The juvenile diabetic patient surviving twenty years. *J. Am. Med. Assoc.* 120: 188. 1942.

The case histories of seventy-three juvenile diabetics of the pre-insulin era are traced to the present time and their medical records analyzed statistically. The most uniform significant finding is the early appearance of arteriosclerosis; 30% showed X-ray evidence of peripheral arteriosclerosis, 55% showed definite ocular arteriosclerosis and 70% of the patients had one or both of the above with either hypertension or albuminurea at the average age of 29 years. Other findings were impaired physical development, hereditary history in 62%, no increased incidence of infection, higher educational attainment, and increasingly favorable survival of offspring.—*C.P.*

FISCHER, A. E., H. S. MACKLER AND H. H. MARKS.

Long term growth of diabetic children. *Am. J. Dis. Child.* 64: 412. 1942.

The literature contains conflicting reports on the height at the onset of diabetes in children and the rate of growth following the development of the disease. Some authors state that diabetic children are tall for their age at the onset of the disease and that later the rate of growth is lower than the average for nondiabetic children. Others report that diabetic children are not above average height at the onset of the disease and do not show any constant trend in height at any time before or after treatment.

The present study is based on the records of 44 under-privileged children, 23 boys and 23 girls; all of whom, except one, were less than thirteen years of age at first observation. The length of time of treatment varied from 5 to 10 years.

The diet in former years contained 20 to 25 per cent carbohydrates, 10 to 15 per cent protein and the remainder in fat. In recent years, this was changed to 40 per cent in carbohydrates, 15 per cent in proteins and 45 per cent in fat. Insulin, crystalline insulin or protamin zinc insulin was administered.

The Burgess scale was used as the height standard, and one inch above the median line was considered as tall and one inch below as short. The children showed the same relationship to their parents' height as do non diabetic chil-

dren. Twenty of 25 boys and 16 of 19 girls were either average or tall at the time of onset of the diabetes.

The average growth for both sexes was generally below that of the normal expectation. The normal growth curve for the girls in the series reached the peak during the 14th year and ceased gradually at about the 17th year. For boys the maximum growth was during the 15th and 16th years, with a cessation of growth at about the 20th year. The figures indicate that diabetic children have about the same spurt of growth during puberty as do nondiabetic. Closure of the epiphyses occurs at the normal time.

There was a tendency for the boys to be underweight and for the girls to be overweight during the years of puberty.—*M.B.G.*

HART, J. F., AND J. R. LISA.
Clinical studies of hypoglycemia. *Internat. Clin.* 4: 97. 1941.

The authors found it convenient to divide hypoglycemia into 2 general groups, the spontaneous and the chronic. The first group takes on decided clinical aspects and requires specific therapy; the second is recognized only by the blood sugar findings and calls for no special clinical consideration. These groups vary in their rate of occurrence. In this series of cases, 1 case was found which could be classified as spontaneous, while a considerable number were seen which could be considered as chronic hypoglycemia. In all, there were 13 cases that could very well be placed in this class. Judging from the study of 21,000 routine fasting blood sugars, values under 70 may be found in about 3 per cent of the population. This is probably too high for true hypoglycemia cases, however, for many that gave low values were found to have normal readings when the tests were repeated. The etiology of the case of spontaneous hypoglycemia presented is uncertain. Of the 13 cases of the chronic type 9 were associated with pituitary disease. Included among these, 1 had a complete ablation of the pituitary body, 2 were definite Froelich's dystrophies, 5 were probably Froelich's disease and 1 gave some evidence of a pituitary tumor. One temporary case appeared following a severe injury to the pancreas and another was noted in a patient with petit mal. The other 2 cases occurred in apparently normal individuals. The symptomatology of the 2 types was found to vary considerably. In the spontaneous form, the outstanding clinical symptom is the epileptiform convulsion, progressive over a period of years, with a course that runs from petit mal to frequent spells of coma which may be maniacal. The sudden return of consciousness following the injection of glucose is peculiar to this condition. The blood sugar picture takes on an erratic pattern with extremely low values associated with the convulsions. The sugar tolerance is usually plateau in form. In the chronic form there are no subjective or objective symptoms. Recognition depends entirely on the blood-sugar examinations. Low to slightly subnormal fasting blood sugars may be found but the low point does not reach the extreme low found in attacks of spontaneous hypoglycemia. Treatment of hypoglycemia depends on the type. In the spontaneous type an early case may be treated with frequent carbohydrate meals or high fat diets. In the late or severe stage more active measures are required. Intravenous glucose must be employed to relieve the convulsions. Since the great majority of cases reported in the literature have been found to be induced by hyperactice adenomas of the pancreas and become permanently cured by surgery, a pancreatic exploration is in order. The case here reported demanded a laparotomy. The surgeon in charge recognized no adenoma in the pancreas at the operation but it is still possible that the tumor was missed. In the treatment of the chronic type with no objectional symptoms there is no readon for therapy. The evidence favors spontaneous cure.—*I.B.*

JACOBSON, S. D., AND R. H. LYONS.
The changes in the blood volume produced by diabetic acidosis. *J. Lab. & Clin. Med.* 27: 1169. 1942.

The hemoconcentration of diabetic acidosis was studied on two patients under controlled conditions. Blood volumes were determined by the method of Gibson and Evelyn. Serum protein was measured by the method of Barbour and Hamilton. CO_2 combining power was measured by the method of Van Slyke and Cullen. After control measurements were taken, while the patients were on a suitable diet and insulin, insulin was discontinued. In patient 1, despite uniform caloric intake, there was a weight loss of 5 kg., of which 1.5 kg. was lost during the first 24 hours with the onset of glycosuria. During the 9 days without insulin there was a 36% decrease in plasma volume. The hematocrit and serum protein concentration increased 30.6% and 21.4% respectively. Patient 2 without insulin for 15 days, there was a 21% decrease in plasma vol-

ume. The hematocrit and serum protein concentration increased 12½ and 20% respectively. The circulatory collapse sometimes found in diabetic acidosis may in part result from the decreased blood volume and venous pressure.—*B.B.R.*

LAWRENCE, R. D.

Three diabetic mongol idiots. *Brit. M. J.* 1: 695. 1942.

It is claimed that the coincidence of diabetes mellitus and mongolian idiocy is herewith recorded for the first time. All three cases were children who had relatives with diabetes, and all responded satisfactorily to treatment with insulin. —*E.B.A.*

LEVITT, A., AND J. P. SCHAUS.

Clinical experience with globin insulin. *Medical Times* 70: 187. 1942.

Treatment of diabetics with regular insulin required a minimum of 3 doses per day and the blood sugar levels fluctuated considerably throughout. Hypoglycemic reactions when present usually occurred 2 to 4 hours after insulin injection. With protamine zinc insulin the majority of patients were controlled with a single dose daily. This dose was less in units than the total amount of regular insulin and the blood sugars were lowest after midnight. Frequently hypoglycemic reactions occurred during the night or before breakfast. Some patients presented local skin reactions. Glycosuria was well controlled. There were, however, considerable fluctuations of blood sugar due to the very prolonged action of this type of insulin—24 to 48 hours. It also required a diet so arranged that the maximum number of calories and amount of carbohydrates were given toward the end of the day when the blood sugar was lowest. Globin insulin exerted its maximum effect in about 8 hours and was almost completely used up in 18 hours. Hypoglycemic reactions when present usually occurred in the afternoon and could be obviated by proper arrangement of diet. The authors believe that globin insulin has a definite place in the management of diabetes mellitus.—*E. Huene* (*Biol. Abst.*).

LISA, J. R., M. MAGIDAY, I. GALLOWAY AND J. F. HART.

Arteriosclerosis with diabetes mellitus. A study of the pathologic findings in 193 diabetic and 2250 nondiabetic patients. *J. Am. Med. Assoc.* 120: 192. 1942.

The authors compared the postmortem findings on 193 diabetic patients with 2250 nondiabetics and found that arteriosclerosis is more frequent and severe in diabetic than in nondiabetic patients. A corresponding stage of arteriosclerosis will appear ten years earlier in the diabetic than in normals. Occlusive accidents are more frequent in diabetics but they cannot be correlated with age. Peripheral arteriosclerosis necessitating amputation is of equal severity in patients with and without diabetes.—*C.P.*

MCKITTRICK, L. S.

Surgical problems in the diabetic. *Pennsylvania M. J.* 45: 559. 1942.

The author reports a series of 1858 operations performed between 1928 and 1941 upon subjects of diabetes mellitus. The mortality rate was 7.8 per cent. Fifty-six per cent of these operations were for gangrene or infection of the lower extremities. Eighty-one operations for gallstones carried a mortality of 6.2 per cent, which compares with a mortality of 3.1 per cent for 286 operations in nondiabetic patients. Between 1923 and 1941, 1036 amputations have been done for gangrene or infection of the lower extremities. Four hundred and twenty-seven or 41 per cent have had an amputation of one or more toes; of these, 348 or 81.5 per cent were successful. The closed supracondylar amputation is recommended as the safest major procedure. This operation has been done 407 times with a mortality of 11.5 per cent. The importance of pulsation in the dorsalis pedis artery as a means of determining the adequacy of the circulation in the foot is stressed.—*Author's Summary.* (*I.B.*)

O'BRIEN, C. S., AND J. H. ALLEN.

Ocular changes in young diabetic patients. *J. Am. Med. Assoc.* 120: 190. 1942.

The author found the high incidence of 4% of retinopathy in a series of 500 diabetic cases less than 21 years of age. Changes in refraction were noted which could be correlated with the institution of insulin therapy. Diabetic cataract was common—occurring in 14% of 260 patients under the age of 21 years.—*C.P.*

OLMSTED, W. H.

Diabetic acidosis. *Med. Clin. N. America* 26: 375. 1942.

This excellent paper on diabetes mellitus in adults must be read in its entirety to be fully appreciated. The cause of diabetic acidosis is the excessive production of such ketone bodies as acetone, diacetic acid, and betahydroxybutyric acid. The first step in the production of ketosis must be the substitution of fat metabolism for carbohydrate metabolism. This occurs during

carbohydrate starvation or when there is a lack of insulin or when the diet is predominantly fat and contains very little carbohydrate. Step 2 consists of an increase in fat mobilization from the depots of the body, with the result that the liver is stuffed with fat and that the metabolism of fat by the liver is tremendously increased. This fat is broken down in the liver through the route of ketone formation. There is a great increase in ketone bodies in the blood. The muscles take care of as much of the ketone production as they can but the ability of the muscle to metabolize ketones is limited in extent, so that the last step is the failure of ketone breakdown to keep pace with ketone formation, with the result that a great rise occurs in blood and body tissue level of the ketones. Acidosis always means dehydration and the 2 conditions go hand in hand. This accounts for the state of shock so often seen in severe diabetic acidosis. The principles of treatment of diabetic acidosis are: 1. the fearless use of large doses of insulin; 2. a time limit of 6 to 12 hours for the control of acidosis and dehydration; 3. the use of intravenous glucose only after the control of hyperglycemia, when carbohydrate cannot be taken by mouth, or in the event of failing circulation, and 4. the use of sodium lactate when a low level of sodium bicarbonate in the plasma persists following the control of hyperglycemia.—*I.B.*

POULSEN, J. E.

Studies on diabetes mellitus. *Ugeskrift f. Laeger* 103: 1220. 1941.

A micro-method for serial-determination of blood ketone was established, and the method given. Investigations of ketonemia in diabetics during fasting and after giving glucose, butter and protein gave varying results depending on the nature of the cases. After insulin injection there was in all cases first a parallel fall in blood sugar and in blood ketone concentration; when the blood sugar fall ceased, there came a rise in blood ketone concentration, especially strong when the blood sugar was brought below 100 mg. per cent. The rise in ketonemia was proportional to the initial value; diabetics without hyperketonemia at the start of the test showed only a very slight rise in ketonemia during the hypoglycemic phase. The course of the blood sugar during coma-treatment should be controlled in that hypoglycemia during this period might aggravate the ketosis. In normals or diabetics, on a diet which at intervals was changed in fats and carbohydrates, but during the test was unchanged as to proteins and calories, there was a close correlation between the fasting blood ketone concentration and the fat content of the diet; highest ketone values were found after diet periods richest in fat. After glucose perorally and insulin intravenously ketonemia fell deeply and only in diabetics on the diet richest in fat was there a rise at the end of the test period. By moderate ketosis and moderate diuresis the Legal's reaction is positive by blood ketone concentrations above 5 mg. per cent and Gerhardt's by values above 10 mg. per cent.—*H. O. Holck* (*Biol. Abst.*).

RICHARDSON, RUSSELL.

Immunity in diabetes. IV. Measurements of phagocytic activity in diabetes mellitus. *Am. J. M. Sci.* 204: 29. 1942.

The phagocytic power of the leukocytes was determined for diabetic patients, pancreatectomized cats and normal controls according to the method of Boerner and Mudd. The diabetic cat and human phagocytosis did not vary from the normal in uncomplicated controlled diabetes. In uncontrolled diabetes or acidosis the phagocytic power was significantly decreased. The diabetic patients did not show the normal increase in phagocytic power which follows typhoid vaccine pyrexia in the normal subject.—*C.P.*

ROCHE, E. H.

Insulin hypoglycaemic coma; with a report of two fatal cases. *Brit. M. J.* 2: 35. 1942.

The first case is that of a 50 year old man who had been treated with a daily dose of 20 units of protamine-zinc-insulin and 16 units of ordinary insulin. Two hours and twenty minutes after discharge from hospital he developed hypoglycemic coma. Forty minutes later intravenous glucose therapy was begun, but although the blood sugar was maintained thereafter above hypoglycemic levels, coma persisted and death occurred in 7 days. The second patient had 24 units of protamine-zinc-insulin each morning at home. Having missed his lunch and suffered a minor automobile accident the patient became comatose at 1:30 P.M. An error in diagnosis prompted the administration of a further dose of 12 units of protamine-zinc-insulin and intravenous glucose was not given until 2¼ hrs. after the beginning of coma. Although the blood sugar was restored and maintained at normal levels, death occurred at 8 o'clock that evening. It is considered that irreversible brain damage resulted from the very low blood sugar levels which were observed in these two cases.—*E.B.A.*

WOODROW, C. E.

Diabetes mellitus and pregnancy. *Brit. M. J.* 1:721. 5942.

A case is described of a mildly diabetic woman whose glycosuria was well controlled with 20 units of protamine-insulin daily until the 5th month of pregnancy. Thereafter the daily insulin requirement fluctuated between 25 and 85 units and this necessitated hospitalization until delivery. As term approached the daily insulin requirement gradually fell. Caesarian section was performed and under the supposition that the infant's pancreas had contributed to the improvement of the diabetic state in the mother, the baby was treated for hypoglycemia.—*E.B.A.*

WOODYATT, R. T., AND MARSEILLE SPETZ.

Anticipation in the inheritance of diabetes. *J. Am. Med. Assoc.* 120: 602. 1942.

One hundred families in which diabetes has been known to occur in two or more generations and in which the ages of onset could be ascertained, were studied for statistical evidence of trends. They rarely found families in which diabetes appeared for more than four generations. Those patients that develop the disease in later life appear as cases of first and second generations. On the other hand, juvenile diabetic patients appear as cases of following generations—they are offspring or expressions of an old family diabetes. The inheritance incidence resulting from the mating of juvenile diabetics can only be settled by the accumulation of more data.—*C.P.*

THYMUS

BROMER, R. S.

Diagnosis and treatment of thymic hyperplasia. *Med. Clin. N. America* 26: 1771. 1942.

This is a brief discourse of the subject with an illustrative case occurring in a male infant 2 months old, which terminated fatally. Among the symptoms attributed to thymic hyperplasia, chronic or paroxysmal stridor and cyanosis are usually mentioned. To these should be added wheezing respiration. The stridor is described by some as inspiratory in nature while others claim it occurs during expiration. A peculiar crowing noise is also mentioned by many writers. Difficulty in swallowing, choking attacks and, in older children, a brassy cough have been placed in the category of thymic symptoms. Attacks of 'holding the breath' are regarded as significant of thymic involvement but there is little if any evidence to support this contention. The author thus summarizes his contribution: The thymus causes symptoms of compression occasionally, but such instances are extremely rare and other causes of compression must be sought before thymic enlargement can be considered the etiologic factor. Certain enlargements of mediastinal structures can cause symptoms of compression which respond to irradiation, but this, too, is of rare occurrence. Great caution is necessary before a statement can be made that roentgenograms show thymic enlargement. It is well to discard the term "status thymicolymphaticus." If the thymus is related to sudden death it is only in a secondary capacity, and there is no treatment of the thymus by injection of any thymic extract, by irradiation, or by its extirpation which would have any effect upon the prevention of sudden death. But 2 roentgen treatments are necessary to accomplish the desired result.—*I.B.*

THYROID

AIRD, R. B.

Experimental exophthalmos and myopathy induced by thyrotropic hormone. *Ann. Int. Med.* 15: 564. 1941.

Exophthalmos was produced in young guinea pigs by injection of anterior pituitary extracts containing thyrotropic hormone. Ocular proptosis developed in the refractory period following the acute thyrotoxicosis, progressed slowly and irregularly during periods of injection and continued during posttreatment periods. Myopathy of extraocular muscles was sufficient to account for appearance of exophthalmos as well as for its permanence following prolonged treatment. It is believed that myopathy of extraocular muscles may account for malignant exophthalmos in human patients.—*D.A.M.*

BARATZ, J. J., AND I. P. BRONSTEIN.

The heart in children with thyroid deficiency. *Am. J. Dis. Child.* 64: 471. 1942.

The authors report the results of cardiac examinations of three children with thyroid deficiency and follow-up notes on their original patient with "myxedema heart." They stress the importance of making routine roentgenograms of the heart and electrocardiographic tracings for children with hypothyroidism both at the beginning and after a period of treatment.—*M.B.G.*

BLOCK, S.

Prolonged thyroid treatment. *Diseases of the Nervous System* 3: 213. 1942.

A brief report is made of the late outcome of three cases of profound childhood myxedema in which treatment began in 1907. Thyroid was administered for a prolonged period in high dosage—up to 50 grains daily. In 1921 the dosage had been gradually reduced to 5 grains daily. The outcome was notably satisfactory, all three subjects having reached and maintained a high degree of normality. The author emphasizes that often heavy endocrine medication will give good results when timid therapy is ineffective; also that thyroid can be given for as long as 34 years without untoward results.—*R.G.H.*

CANTILE, ENRIQUE, AND CARLOS FERNÁNDEZ SPERONI.

Endocrinopathies II. Goiter, exophthalmos and tachycardia in hypothyroidism. *Semana méd.* 48: 973. 1941.

A woman approaching menopause showed bilateral exophthalmos, pale dry skin, fine short hair growth, diffuse hypertrophic thyroid without "thrill," a pulse rate of 104, blood pressure of 100/60, B.M.R.—12. The weight was slightly above normal. Menstruation was scanty and irregular. The treatment consisted in 2 to 3 capsules daily containing thyroid 0.075 gm., total ovarian substance 0.075, gardenal 0.025, theocine 0.1 lactose 0.3 gm. After 8 months almost complete disappearance of the goiter, loss in weight to the ideal figure, reduction of pulse rate to 72, normalization of menstruation and subsidence of the hypothyroid symptoms were noted.—*A.E.M.*

DINE, R. S., AND P. H. LAVIETES.

Serum magnesium in thyroid disease. *J. Clin. Invest.* 21: 781. 1942.

Bound, total, and ultrafiltrable magnesium were determined in 14 normal subjects, 9 patients with untreated hyperthyroidism and 4 patients with untreated myxedema. Total serum magnesium does not vary significantly in the 3 groups. Ultrafiltrable magnesium is abnormally high in patients with myxedema and normal in patients with hyperthyroidism. Conversely bound magnesium is present in only negligible amounts in myxedema and reaches values between 0.6 and 1.0 mg. per cent in hyperthyroid patients. The study of bound magnesium shows practically no overlapping of values as among the 3 groups: myxedema, normal, and hyperthyroid. Bound magnesium in patients with hypermetabolism but without clinical hyperthyroidism fell within normal limits. In 5 of the 6 patients with hyperthyroidism treated with Lugol's solution, the values failed to return to normal levels. Three patients with myxedema controlled by the administration of desiccated thyroid had normal amounts of bound magnesium. The correlation thus established between thyroid function and the state of serum magnesium confirms previous investigators. The reciprocal changes of bound and free magnesium are of unusual interest.—*B.B.R.*

FLEISCHMANN, W., AND H. B. SCHUMACKER.

The relationship between serum cholesterol and total body cholesterol in experimental hyper- and hypothyroidism. *Bull. Johns Hopkins Hosp.* 71: 175. 1942.

Total body cholesterol and serum cholesterol were determined in thyroidectomized rabbits and rats, in rats treated with thyroxine, and in normal controls. Changes in concentration of cholesterol in serum did not parallel changes in concentration of cholesterol in the body. Thyroid hormone influences the shift of cholesterol to and from blood plasma.—*J. V. Scudi* (*Biol. Absts.*).

HILL, A. M., AND J. E. WEBBER.

Hypothyroidism in children. *J. Michigan State M. Soc.* 40: 811. 1941.

Children resistant to preventive treatment for upper respiratory and other chronic infections should be studied for possible metabolic disorders. 'Paradoxical hypothyroidism' may be suspected in children showing irritability, restlessness, hyperactivity, anorexia and small stature. The more common findings in hypothyroid cases are stunted growth, obesity, slowness in school, irritability, fatigue, anemia and constipation. These respond to specific thyroid therapy in the majority of cases.—*D.A.M.*

LERMAN, J.

The treatment of exophthalmic goiter. *Med. Clin. N. America* 25: 1347. 1941.

This is a brief exposition of the author's views on the subject. Since the etiology of Graves' disease is not known, treatment is nonspecific.

Nevertheless, though not an ideal therapeutic approach, symptomatic attention, though imperfect, is for the most part good. As a preliminary to selection of the form of treatment to be adopted, the diagnosis must be confirmed by an evaluation of the history, physical examination and laboratory procedures. Treatment consists essentially of 3 types—surgical, roentgenological, and iodine alone. Fourteen case histories are cited, 10 of which illustrate the results of thyroidectomy. These indicate the need for postoperative vigilance respecting myxedema, recurrence, circulatory disturbances, diabetes mellitus, progressive exophthalmos, tetany and other complications. The author concludes to the effect that iodine alone has proved to be a fairly good form of treatment in selected cases. Roentgen radiation has not been too satisfactory except in patients with persistent or recurrent hyperthyroidism. A few patients with the initial disease do respond to radiation. The knowledge of the regulating action of the pituitary thyrotropic hormone over the thyroid has contributed to its therapy. Those patients whose major complaints center about the eyes should be treated cautiously. Thyroidectomy is usually contraindicated in this type; iodine plus thyroid substance may help considerably.—*I.B.*

MAN, E. B., A. E. SMIRNOW, E. F. GILDEA AND J. P. PETERS.

Serum iodine fractions in hyperthyroidism. *J. Clin. Invest.* 21: 773. 1942.

Using Somogyi's zinc sulphate precipitation technic the serum iodine of 6 normal and 15 hyperthyroid patients was determined. It was shown that in normal patients, receiving Lugol's solution in therapeutic amounts the total serum iodine agreed within 1.6 gamma per cent with the total serum iodine after stopping administration of Lugol's. The precipitable iodine remained quite constant over the entire period of administration, while the filtrate or inorganic iodine rose during Lugol's administration. In the hyperthyroid patients the precipitable or organic iodine fell markedly in response to the administration of Lugol's solution in all but 2 of the 15 patients. The two patients failed to show a drop in basal metabolic rates during the same period. All patients showed normal values after thyroidectomy. Thus the authors suggest that in patients in whom it is difficult to obtain satisfactory basal metabolic rates, the determination of precipitable iodine may offer criteria of diagnostic significance.—*B.B.R.*

MUSSIO-FOURNIER, J. C., AND J. T. FISCHER.

Angina pectoris of thyroid origin. *Arch. clin. inst. endocrinol. (Montevideo) 1, I*: 275 (1937-40).

Angina associated with myxedema occurs in four different clinical variations: 1. Both run parallel and thyroid treatment relieves both symptoms simultaneously. 2. No attacks are experienced during the untreated myxedematous state, but the angina begins with thyroid treatment. 3. The angina coexists with the myxedema, but is aggravated at the rate as the myxedema disappears. 4. The angina disappears at the time when myxedema establishes itself. The thyroid deficiency assumes in this case the rôle of a spontaneous thyroidectomy. In hyperthyroidism the treatment of the angina depends entirely on the reduction of the thyroidal overactivity.—*A.E.M.*

PFAHLER, G. E.

Diagnosis and x-ray treatment of hyperthyroidism. *Med. Clin. N. America* 26: 1751. 1942.

Hyperthyroidism is a condition which concerns especially the general practitioner, the endocrinologist, the ophthalmologist, the surgeon, the radiologist, and, in fact, enters at times as a complicating factor into almost every other branch of medicine. Hyperthyroidism is not synonymous with exophthalmic goiter. Hyperthyroidism is a prominent and probably the leading symptom of exophthalmic goiter, but one may have a severe grade of hyperthyroidism without either exophthalmos or goiter. Furthermore, hyperthyroidism may be only a part of a general disturbance of the endocrine system. The treatment of hyperthyroidism does not consist merely of treating the thyroid either by irradiation or operation, but the predisposing and exciting causes should be removed, and after active local treatment, the patient should be guided and guarded by competent medical advice. Normal thyroid tissue and normal parathyroid tissue are resistant to irradiation and will not be affected by the amount of irradiation needed to control hyperthyroidism. Irradiation with either roentgen ray or radium may be accepted as a useful method of treatment of hyperthyroidism, since the end-results are approximately equal to those obtained by surgery. The fear of operation or delays preceding operation are likely to lead to cardiac enlargement. This delay can be eliminated by the use of irradiation therapy. Irradiation therapy does not involve shock or great inconvenience. Associated medical care and general directions for conservation of energy are essential. Irradiation is probably of value in the prevention of the development of carcinoma.—*I.B.*